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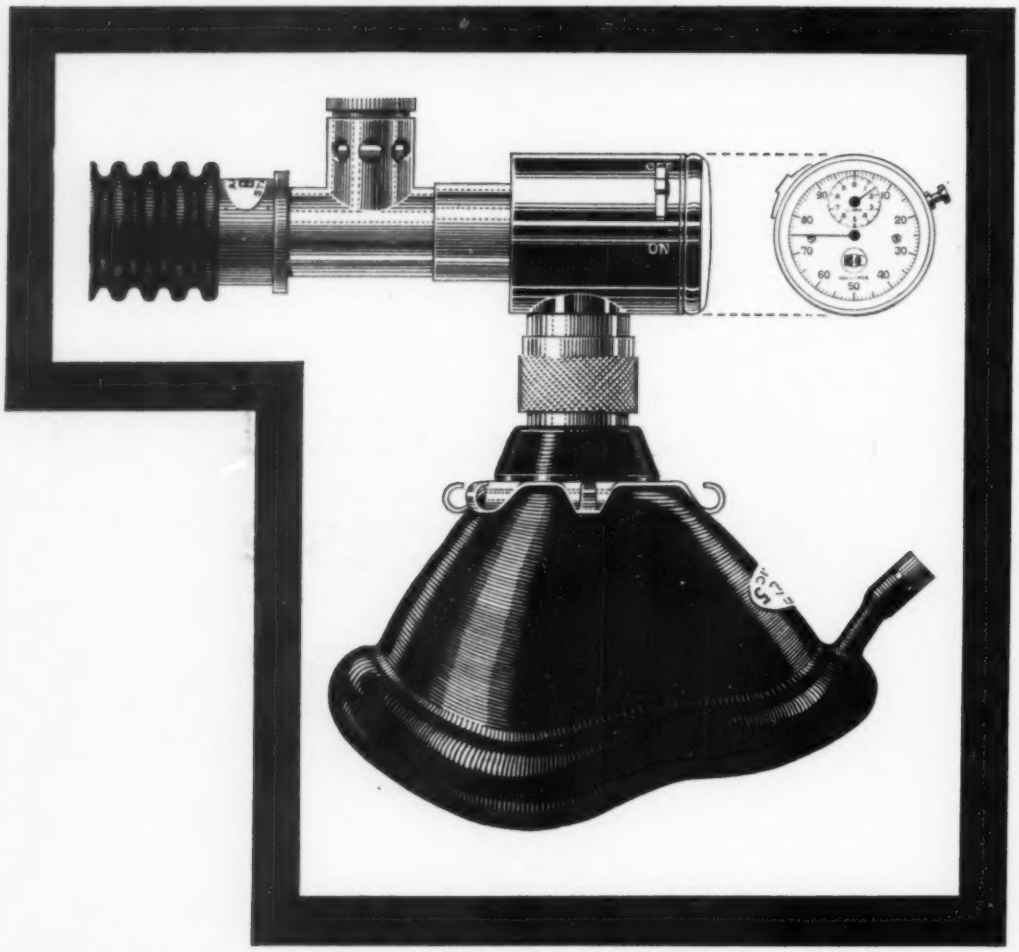

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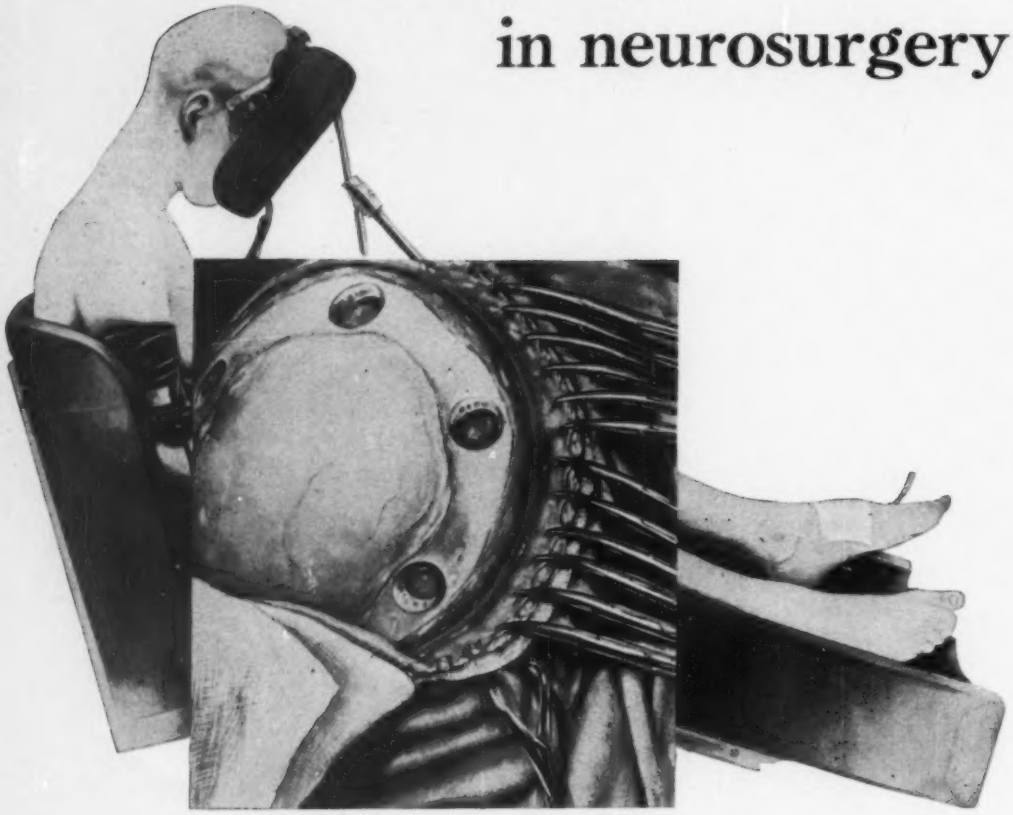

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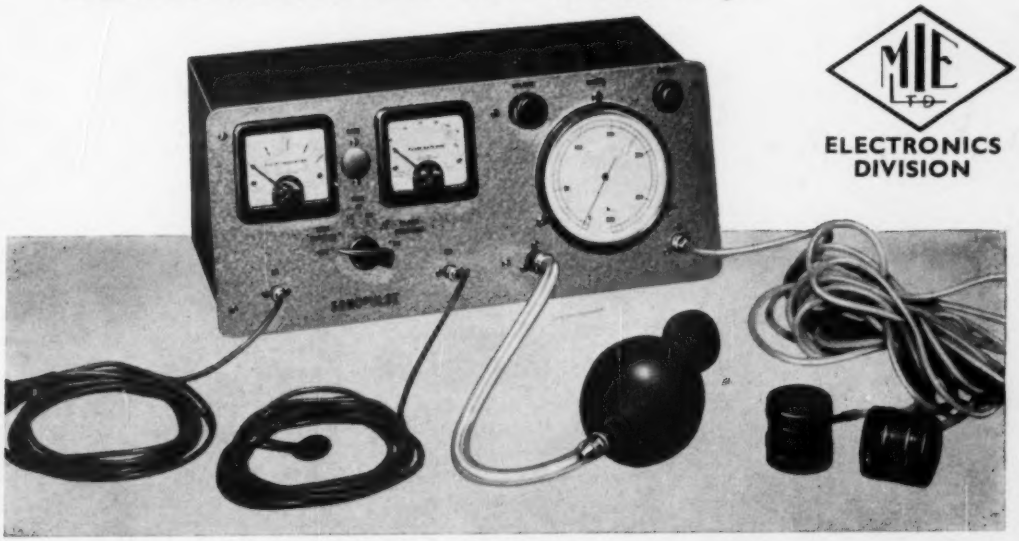

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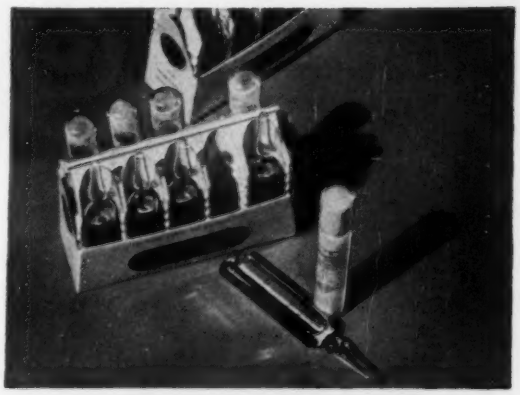

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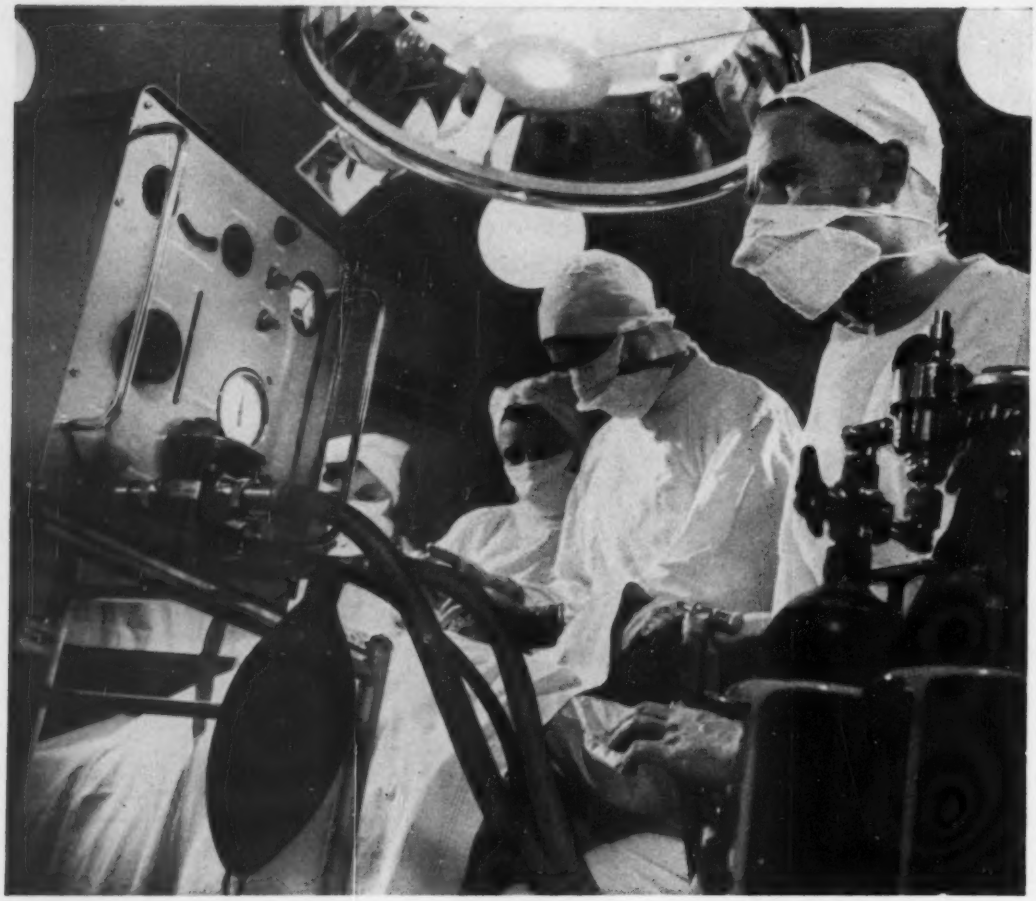

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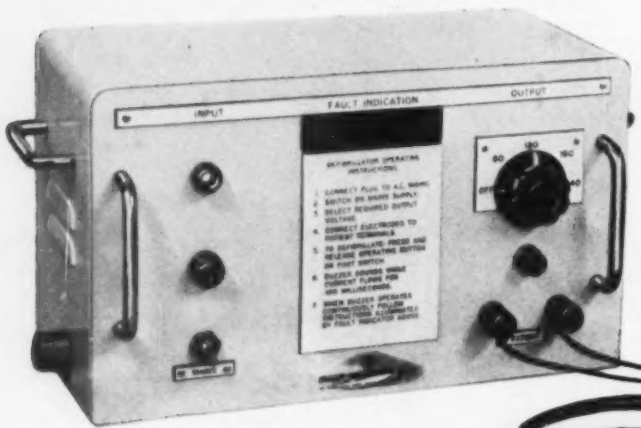

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXXIII, No. 6 JUNE 1961

EDITORIAL

THE recent decision of the Ministry of Health to plan hospital services for ten years ahead will be welcomed by all concerned. It is hoped that planning will not end with thoughts of bricks and mortar. Planned expansion of personnel services is also required so that when new buildings have been completed there will also be available the necessary consultants to staff them. This need applies particularly to the specialty of anaesthesia.

It has long been known that there were too few consultant anaesthetists. As the report of the Working Party on Medical Staffing in the Hospital Service makes clear, part of the reason for this lies in the fact that the numbers in the senior registrar grade are inadequate. In some regions this difficulty was aggravated in 1951 by cuts imposed on the senior registrar establishment though the overall number in this grade in the country as a whole was not then reduced. In consequence there has for some years now been a lack of sufficient trained men to meet the expanding need for consultant anaesthetists, and in less attractive parts of the country there have frequently been no applicants for such posts. Some regional boards, faced with the alternative of a breakdown of the service, have, as they have every right to do under the terms of their agreement with the profession, appointed S.H.M.O.s to do the work, though obviously aware that it really calls for a consultant. There is no shortage of applicants for these posts. They are therefore readily filled, usually by men with long experience but without the Fellowship of the Faculty. Such a state of affairs can do nothing but harm to the regard in which the specialty of anaesthesia is held; yet the ready availability of applicants must encourage those charged with the duty of maintaining the service to use this expedient again.

The obvious remedy is planning for some years ahead, not only of new buildings but for the appropriate staff for them. In an undermanned specialty like anaesthesia this means a planned expansion of the training grade which may in fact be only temporary during the period of need so that when additional consultants are required there will be men trained and ready to apply for the posts.

The existing concept of a senior registrar establishment related to the probable need for replacement of retiring practitioners plus a fixed percentage to allow for emigration and other needs is proving somewhat too rigid to meet the needs of specialties in a period of rapid expansion. In anaesthesia particularly there is need for a new approach to these problems. It is hoped that the annual review of the establishment in the senior registrar grade suggested by the Working Party "in consultation with representatives of the profession . . . and with specialty associations" will meet this need.

Brit. J. Anaesth. (1961), 33, 278

THE NEUROMUSCULAR BLOCKING PROPERTIES OF CERTAIN TROPINE DERIVATIVES

BY

J. P. PAYNE

Department of Anaesthetics, Hammersmith Hospital and Postgraduate Medical School of London, London, W.12

ALTHOUGH suxamethonium chloride is widely used in clinical practice it has a number of disadvantages. Firstly, the incidence of after-pains is high and in some instances they may be severe (Churchill-Davidson, 1954). Secondly, the muscarinic actions of suxamethonium can be troublesome in the absence of atropine or when the dose has been inadequate, and particularly in young children the bronchial secretions resulting may seriously interfere with the administration of the anaesthetic. Thirdly, the occasional occurrence of prolonged apnoea after suxamethonium in the absence of a suitable antagonist can be a serious hazard. Finally, in a few patients intravenous suxamethonium may be followed by cardiac depression and even by inhibition (Johnstone, 1955). There is therefore a need for a more specific short acting, readily reversible neuromuscular blocking agent.

A series of bis-quaternary tropines examined by Haining et al. (1959, 1960) showed promise; two in particular, DF.596 and DF.648, seemed worthy of further study and preparatory to a clinical trial the drugs were investigated in cats.

These drugs consist of two tropine nuclei joined together through the nitrogen atoms. In the case of DF.596 two molecules of the phenyl acetyl ester of tropine are linked and in DF.648 two molecules of the phenyl ether of tropine (Haining, personal communication).

METHOD

Healthy unselected cats were used in the experiments in two groups of three. After induction with ethyl chloride and ether, the right external jugular vein was isolated and cannulated and anaesthesia continued with intravenous chloralose (80 mg/kg). A tracheal cannula was inserted to facilitate artificial respiration during the administration of the relaxant drug. The blood pressure was measured by means of a glass cannula placed in the left common carotid artery and connected to a mercury manometer recording on smoked paper.

The tendon of the right anterior tibialis muscle was avulsed from its insertion and attached to a flat steel spring myograph also recording on the smoked paper. The tendon of the soleus muscle was dealt with similarly after the muscle itself had been gently separated from the overlying gastrocnemius without disturbing its blood and nerve supply. The sciatic nerve was then mobilized, crushed and tied as far proximally as possible to avoid damage to its blood supply. Indirect stimulation of the muscles was achieved by means of a square wave pulse of 0.5 m.sec duration and a strength of 1 to 3 volts applied to the nerve through shielded platinum electrodes at 10-second intervals.

Both drugs were dissolved in physiological saline in a concentration of 0.1 g per cent. All injections were made into the external jugular vein by the divided dose technique recommended by Paton and described elsewhere (Payne and Rowe, 1957). Other drugs used in the experiments were decamethonium, gallamine and neostigmine given intravenously and 5 per cent carbon dioxide in oxygen given by inhalation.

RESULTS

Both DF.596 and DF.648 produced neuromuscular block of comparable duration and extent with approximately the same dose. Almost total block was obtained with a single dose of 400–500 μg and with such a dose the effect was maximum within 40 to 60 seconds and recovery apparently

complete 5 minutes later. The degree of block obtained was greater in the anterior tibialis muscle than soleus and occurred more rapidly; further, the soleus muscle recovered more slowly. Accordingly the dose response was assessed against the anterior tibialis.

With DF.648 paralysis occurred without initial stimulation in all three cats (fig. 1), but in two of the three cats given DF.596 there was a transient increase in twitch size before neuromuscular block was established (fig. 2). This was only seen after the first injection in any one series of injections and with successive series became progressively less prominent, disappearing completely about the fourth or fifth. Neostigmine antagonized the neuromuscular blocking action of both drugs, DF.596 more effectively than DF.648 (figs. 3 and 4). When given in the presence of decamethonium both drugs at first produced a transient slight increase in the degree of block followed by

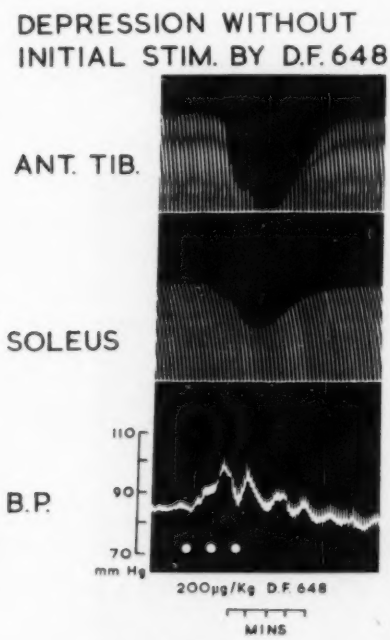

FIG. 1

Cat, chloralose; showing depression of muscle twitch and transient increase in blood pressure after injection of DF.648.

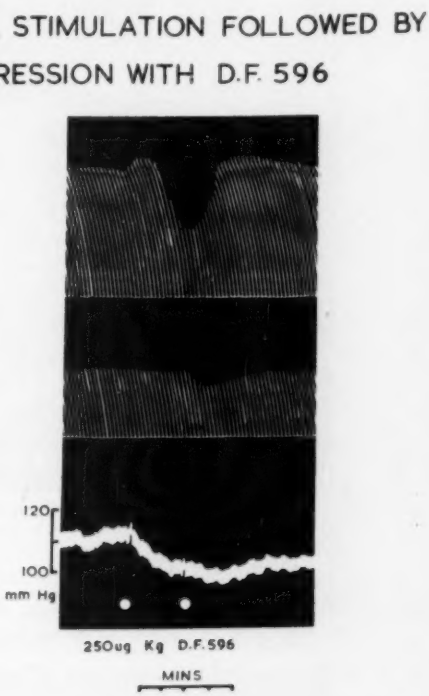

FIG. 2

Cat, chloralose. Upper tracing shows the onset of neuromuscular block preceded by transient increase in twitch size of anterior tibialis muscle after intravenous injection of DF.596. Middle tracing shows the response of soleus muscle twitch and lower tracing demonstrates the slight hypotension associated with the drug.

antagonism as shown in figures 5 and 6. With later doses, however, the blocking effect became more marked and the antagonism disappeared. In the presence of gallamine the effect of both drugs was enhanced both in extent and duration of block (figs. 7 and 8). A tetanus was not sustained during recovery from DF.596 or DF.648.

During the administration of 5 per cent carbon dioxide the neuromuscular blocking properties of both tropine derivatives were enhanced as was reported in detail elsewhere (Payne, 1960a).

As distinct from the neuromuscular blocking effect, the blood pressure response differed with both drugs. When DF.596 was injected intravenously there was invariably a fall in blood

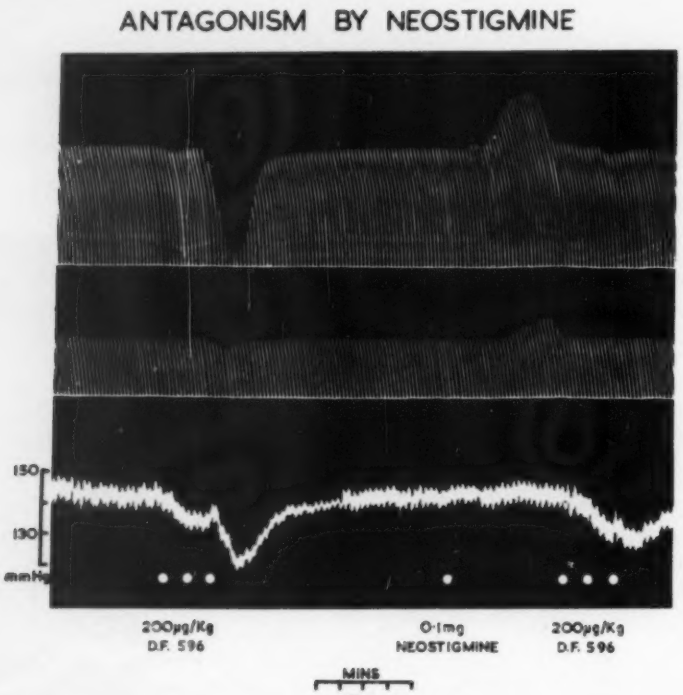

FIG. 3

Cat, chloralose. Shows the anticholinesterase action of neostigmine and its antagonism to the neuromuscular blocking action of DF.596.

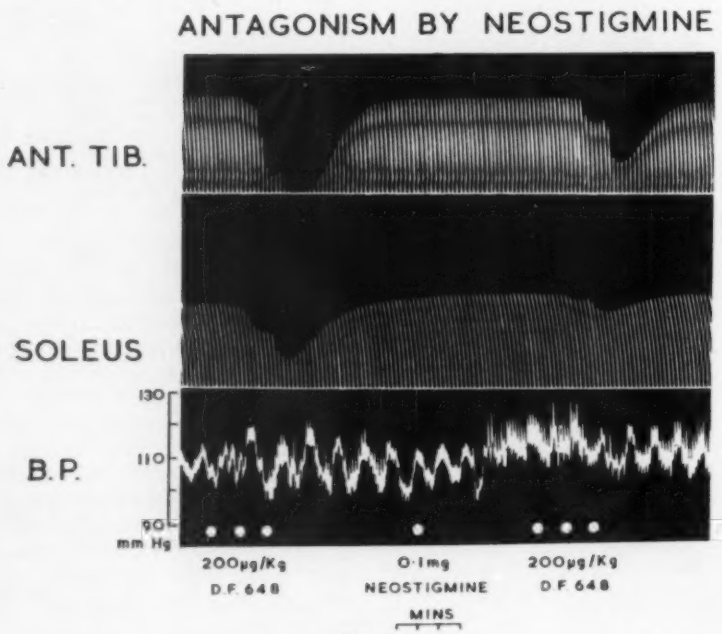

FIG. 4

Cat, chloralose. Shows the ability of neostigmine to antagonize the neuromuscular blocking action of DF.648.

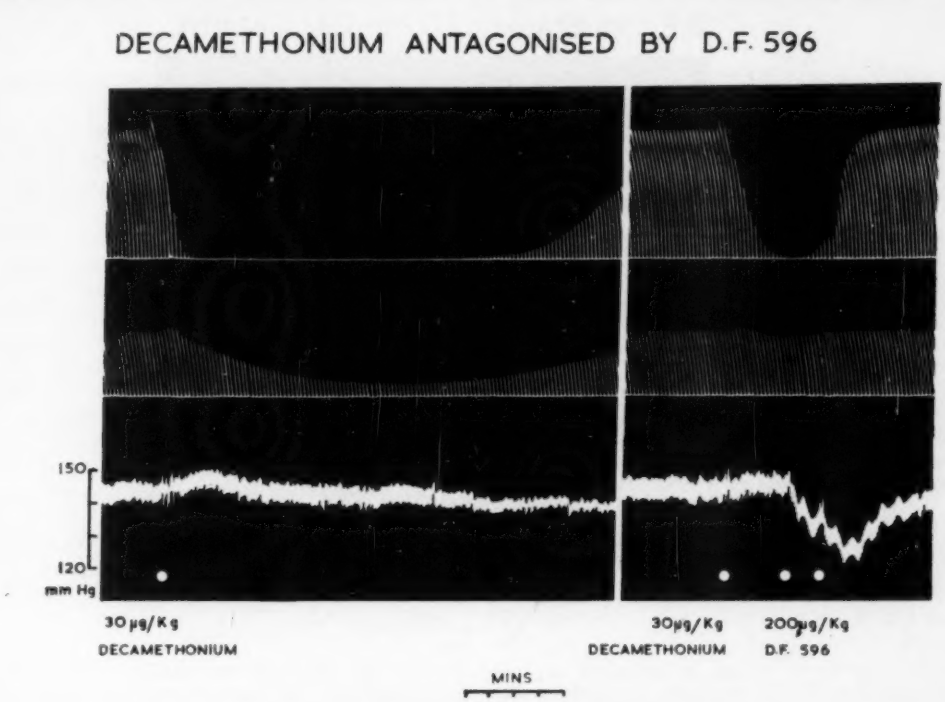

FIG. 5

Cat, chloralose. Antagonism to neuromuscular blocking action of decamethonium by DF.596.

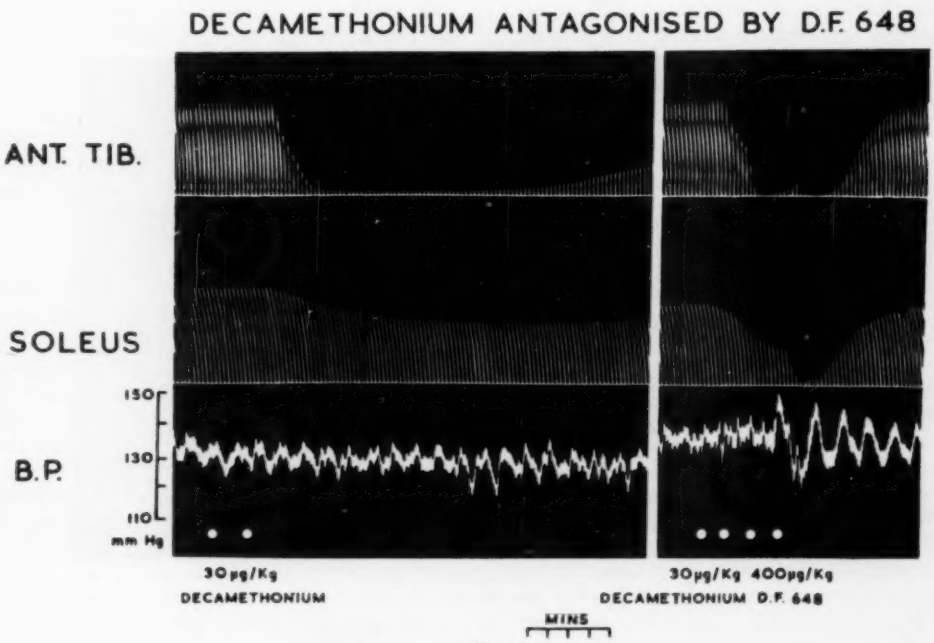

FIG. 6

Cat, chloralose. Antagonism to neuromuscular blocking action of decamethonium by DF.648. Note the transient enhanced effect before the development of antagonism.

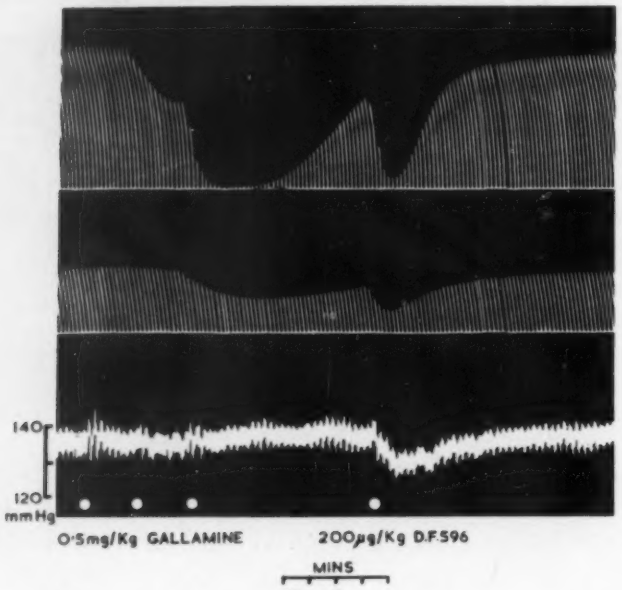

FIG. 7

Cat, chloralose. A single injection (not shown) of DF.596, 200 µg produced no perceptible diminution in the size of soleus twitch and a 12 per cent depression of anterior tibialis. The illustration shows the enhanced effect produced when DF.596 is preceded by gallamine.

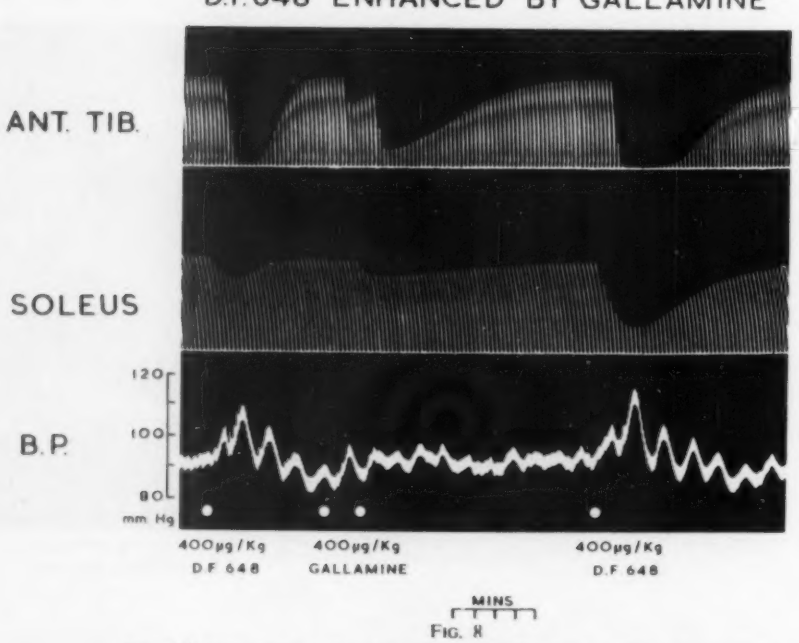

FIG. 8

Cat. chloralose. The enhancing effect of gallamine on the neuromuscular blocking properties of D.F.648.

pressure. The fall was moderate and did not exceed 30 mm Hg. On the whole the degree of hypotension obtained was constant for each animal, except that during the administration of carbon dioxide the hypotensive effect was less marked. DF.648 produced a fall of blood pressure in only one cat; in the remaining two there was a consistent sharp rise which was, however, neither excessive nor sustained. Again the response was reduced during the administration of carbon dioxide.

Associated with changes in blood pressure, pupillary changes were observed. With DF.596 the pupils became widely dilated momentarily but returned to the residual state within a minute of the last injection. When DF.648 was given the pupils were seen to constrict markedly but again this was a temporary effect which disappeared as the blood pressure returned to normal.

DISCUSSION

The results indicate that DF.596 and DF.648 can produce neuromuscular block similar in rate of onset, duration of action and recovery period to that of suxamethonium; but to obtain such comparable effects a dosage ten to fifteen times greater than the dose of suxamethonium was required.

The nature of the neuromuscular block induced by these tropine derivatives was different from that of suxamethonium. It followed the pattern of competition blockers; the action of the drugs was antagonized by neostigmine and decamethonium, enhanced by gallamine, and a tetanus was not sustained in their presence. But their actions were not altogether characteristic of competition block.

Unlike tubocurarine but like depolarizing drugs, DF.596 and DF.648 were more effective on the anterior tibialis muscle than on soleus. Further, the fact that the action of decamethonium was initially enhanced before antagonism developed was unusual. Even more atypical was the gradual extension of this synergism and the progressive but incomplete elimination of antagonism with successive doses. This, however, may well reflect a change in the action of decamethonium rather than in that of the tropine derivatives, particularly as such a change from depolarization to competition block has already been proved for nicotine (Paton and Perry, 1953) and there is strong evidence that it also occurs with decamethonium (Zaimis, 1953), while it has still to be shown that the competitive blocking action of a drug can be succeeded by depolarization block. But the reverse is not true and the possibility exists that the tropine derivatives initially and transiently depolarize before blocking by competition.

At first sight the brief stimulating action of DF.596 before the onset of paralysis would not be regarded as typical of competitive blocking agents but it has been shown that many such drugs, including gallamine (Riker and Wescoe, 1951; Payne, 1958) and tubocurarine (Payne, 1961), may behave in the same way. The transient initial stimulation, therefore, cannot be regarded as evidence against competition block.

The enhanced effect of the drugs in the presence of carbon dioxide was also unusual; in cats most relaxants are antagonized by carbon dioxide though tubocurarine is an exception (Payne, 1958; 1960a). It was originally thought that this enhanced effect of tubocurarine was due to ionization changes in the tubocurarine molecule (Payne, 1959) but this has not been substantiated (Payne, 1960b). Similarly, according to Haining (personal communication) it is unlikely that exposure to carbon dioxide could influence the dissociation of either tropine molecule. The explanation has still to be found.

Although the mechanism of the blood pressure responses was not specifically investigated, there is little doubt that this is a ganglionic effect. The pupillary changes reported support this interpretation and the fact that a closely related substance, phenactropinium chloride has been used clinically as a ganglion blocking agent (Robertson, Gillies and Spencer, 1957) adds further confirmation.

It is clear that the ganglionic effects of these particular tropine derivatives will prevent their use clinically but there seems no reason to doubt that among the many analogues one will be found to match up to the established criteria for a short acting rapidly reversible muscle relaxant. Moreover, the fact that these drugs react a little differently from other relaxants adds to the accumulating knowledge on neuromuscular block, and in particular the initial stimulating action described and the

complex relationship with decamethonium may prove to be useful clues in the final analysis of the neuromuscular blocking mechanism.

SUMMARY

Competition block by tropine derivatives DF.596 and DF.648 has a similar mode of onset, duration of action and recovery period to suxamethonium, but they are unlikely to be used clinically because of their tendency to alter the blood pressure probably by ganglionic action.

Two observations were made which may be of experimental importance: (*a*) DF.596 produces a transient stimulating effect on the muscle twitch before the onset of neuromuscular block; (*b*) both drugs briefly enhance the action of decamethonium before antagonizing it, the effect becoming more marked with successive doses

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Brit. J. Anaesth. (1961), **33**, 285

THE INITIAL TRANSIENT STIMULATING ACTION OF NEUROMUSCULAR BLOCKING AGENTS IN THE CAT

BY

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AN initial transient increase in the size of the muscle twitch before the onset of paralysis has been described as characteristic following the intravenous injection of a depolarizing neuromuscular blocking agent. During several series of experiments undertaken in the study of different aspects of neuromuscular block this typical response was confirmed, but it was also noted that occasionally a similar brief stimulant effect followed the intravenous injection of competitive blocking agents. The observation was sufficiently interesting to justify an examination of all records in an attempt to explain this rather unexpected finding.

MATERIAL AND METHOD

The analysis of previous records was made easy by the fact that a standard technique for the administration of relaxants had been adopted throughout all the experiments. The results obtained were therefore comparable. The method was as follows. All experiments were performed in cats; after induction with ethyl chloride and ether, anaesthesia was established with intravenous chloralose. A dose of 80 mg/kg was injected through a cannula in the right external jugular vein in a strength of 10 mg/ml. The same cannula was used for the injection of the relaxant drug dissolved in physiological saline. A tracheostomy was established to facilitate ventilation with a positive pressure respirator.

After the sciatic nerve had been located in the posterior aspect of the thigh, it was crushed and tied as far proximally as possible to avoid interference with its blood supply. Its medial division was dealt with likewise. The tendon of the right anterior tibialis muscle was avulsed from its insertion and attached to a flat steel spring myograph recording on smoked paper. The animal was placed in a supine position with the right leg horizontal and held rigidly by a drill inserted immediately above the ankle joint. The muscle was stimulated indirectly once every 10 seconds by a square wave pulse of 0.5 m.sec duration applied to the nerve through platinum electrodes at 1–3 volts.

The muscle relaxants covered by this survey were tubocurarine and dimethyl-tubocurarine, gallamine, benzoquinonium, laudexium and mecamylamine, as well as two tropine derivatives DF.596 and DF.648 and suxamethonium and decamethonium.

RESULTS

As was to be expected, initial stimulation was most marked with the depolarizing agents suxamethonium and decamethonium. In 12 cats given suxamethonium the effect was observed in all of them but it was also noted in 7 of the 12 that there was a progressive decrease in the extent of the initial stimulation with successive series of injections. Transient increased twitches were noted in all 8 cats given decamethonium and, of these, 6 showed a progressive decrease in the amount of activity with successive series of injections.

Among the competitive blocking agents, tubocurarine was given to 13 cats of which 3 showed evidence of initial stimulation. In those 3 animals the effect was noted after the first injection and was not seen again. The pattern was similar when dimethyl-tubocurarine was used, although the percentage showing initial stimulation was greater as it appeared in 4 out of 8 cats. The incidence of the response was even higher with gallamine; of 20 cats tested 13 showed a transient enhanced

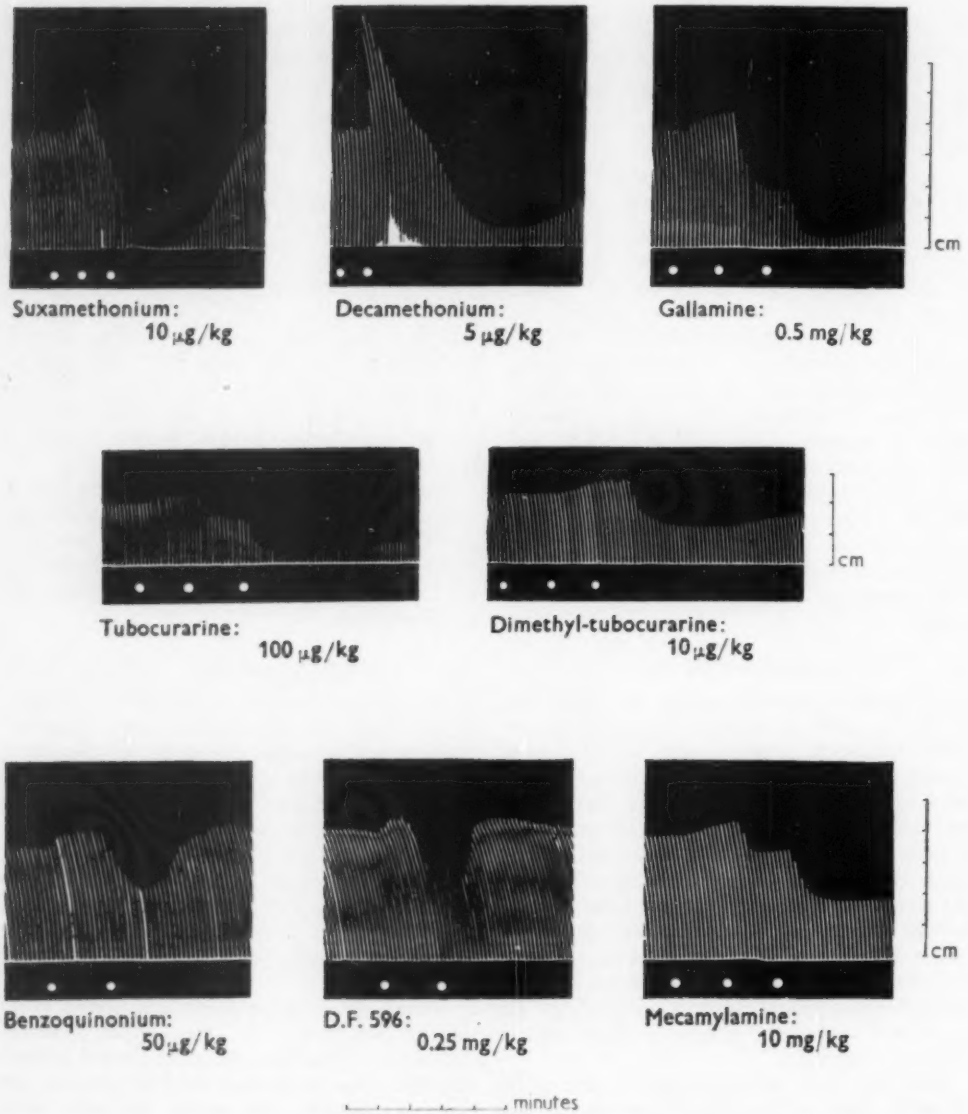

FIG. 1

Showing the transient increase in the size of the anterior tibialis twitch before the onset of neuromuscular block.

effect before the onset of paralysis on the first injection only. Benzoquinonium was used in 2 cats only and both showed a brief initial increase in twitch size before paralysis developed during the first series of injections. In 2 of 3 cats given DF.596 there was a transient increase in twitch size before neuromuscular block became established. With subsequent series of injections it was still apparent but became progressively weaker and disappeared about the fourth or fifth series.

Mecamylamine is used primarily for its ganglion blocking effect but in large doses it has a weak neuromuscular blocking action of competitive type. In 8 cases given this drug all showed a transient increase in activity before the onset of paralysis.

Laudexium was given to 3 cats as was DF.648 but no evidence of initial stimulation was seen with either drug.

DISCUSSION

It has previously been reported without comment that the intravenous injection of gallamine into the cat may be followed by a brief initial increase in excitation before the onset of paralysis (Riker and Wescoe, 1951; Payne, 1958). The work described here establishes that such a stimulation is not uncommon after the first injection of most competitive blocking agents. Such an observation is hard to understand if the classical interpretation of competition block is accepted in its entirety and any attempt to do so is complicated by the fact that the analysis of the problem must prove difficult if for no other reason than that in most instances the effect is seen once only in any one animal.

However, the facts reported are in accordance with the theory of drug action recently propounded by Paton (1960) which suggests, (1) that the stimulant action of a drug is dependent on the rate of its combination with tissue receptors; (2) that the stimulant action is maximal on first exposure when all receptors are free from combination with the drug; later the presence of occupied receptors will slow down the rate of combination and thereby reduce or abolish it; (3) that when dissociation of the drug from receptors is slow the stimulant effect is correspondingly feeble; (4) that for any antagonist its initial combination should lead to some degree of excitation not necessarily detectable.

This theory explains why stimulation occurs, why it is most marked with the first injection, why it is weaker with some drugs than with others and why in some instances no stimulant action is seen. The theory also implies that strictly speaking there is only a quantitative and no qualitative difference between drugs classified as depolarizers and competition blockers although the quantitative differences may be very large. In particular it excludes the use of the terms "antidepolarizer" and "nondepolarizer".

The theoretical considerations are substantiated by considerable experimental and clinical evidence in favour of a transition from depolarization to competition block.

In 1953 Paton and Perry showed that, when nicotine was used to block the superior cervical ganglion in the cat, they could obtain direct electrical evidence of a change from depolarization to competition block. Later, Zaimis (1953) showed that in the dog, hare, monkey and rabbit the nature of depolarization block with decamethonium was changed with time and repeated dosage so that the block was ultimately antagonized by neostigmine and tetanic stimulation and enhanced by tubocurarine. In man, Brennan (1956) demonstrated that in a series of 62 patients given suxamethonium by continuous infusion, neostigmine antagonized and gallamine enhanced the neuromuscular block in most patients. The transition was gradual and seemed to be related to the duration of exposure and dose of drug employed. By demonstrating that the prolonged administration of either suxamethonium or decamethonium sensitized the motor endplate to the effects of d-tubocurarine and gallamine in the dog, cat and man, Foldes et al. (1957) confirmed and amplified the findings of Zaimis and Brennan.

There is no evidence to suggest that competition block ever precedes depolarization block.

An increase in the size of individual muscle twitches may result from cholinesterase inhibition and as many relaxants possess anticholinesterase activity (Foldes, 1957) this offers an alternative explanation. But the evidence that inhibition of cholinesterase occurs in vivo with the doses employed here is not convincing and the inability in most instances to demonstrate enhanced activity

with other than the first injection does not support this interpretation.

The possibility of other factors such as the influence of the drugs on the nerves and muscles as distinct from the motor endplate has to be considered. In the dosage used there is no known action of relaxant drugs on nerve fibres and spinal reflex activity can be excluded because the nerve was crushed and tied proximal to the point of stimulation. This, of course, does not exclude axon reflexes but the nature of the response makes it unlikely that such reflexes are involved.

The behaviour of muscle fibres can be altered by drugs and could conceivably produce the effect described, but again it is difficult to understand how the activity could be altered so consistently and yet so rarely under the conditions of the experiments.

SUMMARY

The division of relaxants into depolarization and competition blockers is less well defined than had previously been believed and evidence has been presented which, though not conclusive, suggests that all neuromuscular blocking agents pass through a depolarizing phase which is later followed by competition block if the action of the drug is prolonged. The depolarizing phase is extremely short with drugs like tubocurarine and competition block develops early, but with decamethonium and suxamethonium competition block may never be seen unless the block is unduly prolonged.

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F.F.A.R.C.S.I.

The first examination for the Primary Fellowship of the Faculty of Anaesthetists of the Royal College of Surgeons in Ireland will commence on November 13, 1961. Entries must be lodged with the Registrar R.C.S.I., St. Stephen's Green, Dublin 2, twenty-one days beforehand.

Brit. J. Anaesth. (1961), **33**, 289

THE USE OF AIR IN ANAESTHESIA: VENTILATION MEASUREMENTS DURING ANAESTHESIA WITH AIR AND THE HALOTHANE-ETHER AZEOTROPE

BY

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PARKHOUSE and Simpson (1959) have suggested that air as a vehicle for anaesthetic vapours is ideal and should be used extensively. They discuss the virtues of the technique, particularly in regard to simplicity and state that cyanosis is a good warning of inadequate ventilation. They believe that carbon dioxide levels of twice normal are not seriously harmful in most cases. This view is shared by Nunn (1959), who believes that tensions below 70 mm Hg are probably harmless. Fit patients can survive tensions up to 150 mm Hg, but Nunn warns that carbon dioxide retention may be a hazard when the patient is returned to the ward. Poppelbaum (1960) maintains that the use of air is quite feasible with controlled respiration, although there is a big fall in arterial oxygen saturation during the apnoeic period of intubation, and that in spontaneous respiration desaturation readily occurs. Nandrup (1959) has shown that during ether-air analgesia normal saturation was maintained and low Pco_2 levels recorded. In fact, his patients were hyperventilating. Faulconer and Latterell (1949) demonstrated that desaturation did occur while using ether-air and that possibly the diluent effect of up to 14 per cent of ether vapour was partly responsible. They recorded saturations as low as 70 per cent but small amounts of added oxygen improved the saturation levels. Ikezono, Harmel and King (1959), again using ether-air anaesthesia, showed that desaturation does occur and that assistance to respiration was desirable. They produced quite satisfactory saturation with controlled respiration but not when the patient was breathing spontaneously; partly because of the unsteady state, and the long respiratory pauses if respiration was irregular. Bryce-Smith and O'Brien (1956), using air and halothane observed cyanosis frequently and had to assist respiration. At one stage a minute volume as low as 1.2 l. was recorded.

Most workers appear to agree that air is satisfactory for use during controlled respiration but that spontaneous respiration leads to desaturation. With an unsteady state desaturation will occur rapidly if there is a small oxygen reservoir in the lungs. Weitzner, King and Izekono (1959) showed that dangerous desaturation occurs after $1\frac{1}{2}$ minutes of apnoea when air is breathed but with a high oxygen concentration in the inspired gases no desaturation occurs after 2 minutes or more. Cyanosis is observed often by anaesthetists using air and this may not occur until the saturation falls to 70 per cent. It is generally accepted as an unreliable guide to adequate ventilation (Comroe and Botelho, 1947; Scurr, 1956a: Medd, French and Wyllie, 1959), so that usually the appearance of cyanosis means gross underventilation. Nevertheless, it is sometimes held that all anaesthetized patients breathing spontaneously are underventilating; the use of air may only reveal what is normally masked by higher oxygen concentrations and these need not be very much higher than in air. A small increase in oxygen tension will give a very large increase in saturation when the increase occurs on the steep part of the oxygen dissociation curve. In the Services, the use of air instead of stored gases has been, and could be, of great value during supply difficulties. An investigation was carried out using air and the azeotropic mixture of ether and halothane. The object was to decide if the method had any place in anaesthesia under conditions of gas cylinder shortage, or if desaturation was too common and too severe to justify its use. The halothane-ether azeotrope is probably ideal for use with air. Dobkin, Drummond and Parkin (1959) have

extensively reviewed this mixture and have shown that it causes less hypotension and fewer cardiac irregularities than does halothane alone and provides smooth and stable anaesthesia. The explosion risk is controversial (Dobkin, Drummond and Parkin, 1959; Raventós and Dee, 1959) but with air, up to 3 per cent of the mixture is required and this implies an ether concentration below the explosive range. Initially in this hospital the mixture was used with nitrous oxide and oxygen for various patients, particularly those undergoing ear, nose and throat operations, and it was found to be most satisfactory. When used with air cyanosis was seen frequently at first but as experience was gained it was possible to provide adequate anaesthesia with the patient apparently well oxygenated. A quantitative series was attempted.

METHOD

Eighteen patients undergoing minor operations, such as for the repair of hernia, were premedicated with papaveretum 20 mg and hyoscine 0.4 mg. Anaesthesia was induced with thiopentone 300 to 450 mg and intubation was carried out using suxamethonium. When spontaneous respiration was established, the patient was connected via a Ruben valve to a machine which has a gravity drawover valve and a vaporizer with a heat exchanger consisting of blackened alloy fins (Soper, in preparation). A compensating double cell type of oximeter was applied to an ear and the outlet side of the Ruben valve was connected to a Wright ventilation meter. Serial readings of minute volume and oxygen saturation were taken at 5-minute intervals and arterial Pco_2 estimated before the patient was returned to the ward.

Ventilation standards.

Some indication of desired ventilation was required. The Radford nomogram (Radford, 1955) has been suggested for use during anaesthesia (Scurr, 1956a; Nunn, 1960). Nunn and Matthews (1959) have shown that the oxygen consumption during anaesthesia is decreased by 15 per cent and in a steady state it follows that the carbon dioxide production is likewise decreased. Nunn (1960) found that the Radford nomogram was a reliable guide in the steady state, as the physiological deadspace is increased by 15 per cent and thus tends to cancel the decreased carbon dioxide production. Difficulties were encountered in the unsteady state but he assessed the nomogram as a satisfactory guide to a reasonable standard of ventilation. He also showed that during anaesthesia the alveolar ventilation is a constant fraction of the minute volume. In spontaneous respiration this factor is 0.7. Accordingly, a modification of the Radford nomogram was drawn; first plotting alveolar ventilation from the formula: $\dot{V}_A = f[V_T - V_D]$. Deadspace was assumed on the basis of 1 ml/lb. body weight (Campbell and Dickinson, 1960). The values between respiratory rates of 12 and 18 per minute were equal for appropriate weights and show a linear relationship to body weight. Predicted ventilation in anaesthesia is drawn related to alveolar ventilation with a factor of 0.7. Minute volumes of total ventilation were plotted on the same graph for comparison (fig. 1). The values for alveolar ventilation compare favourably with the original figures of Harris and Benedict (1919).

Wright (1958) claims that the ventilation meter is reasonably accurate when a calibration factor based on a sine curve pump is used but Cooper (1959) points out the defects in this type of meter. However, for clinical purposes it is accurate enough, particularly with spontaneous respiration, and provided flows are not too low. Byles (1960) has shown that the Wright meter has an error of less than 7 per cent with reasonably normal flow rates.

Carbon dioxide levels were estimated at the end of anaesthesia, as retention after the patient has left the theatre is probably more hazardous than during surgery. Moreover, with the method available serial Pco_2 measurements during anaesthesia are not easy to undertake. The Pco_2 was estimated by the rebreathing method (Scurr, 1956a; Campbell and Howell, 1959), analysis of the bag carbon dioxide being made with a Dräger analyzer (Lawes, 1956; Nunn, 1958) under the conditions stipulated by Nunn (1958). Sykes (1960) has modified this method but on a series of controls it was found to be reasonably accurate using the original Campbell and Howell routine.

The oximeter was found to be consistent if calibrated at 100 per cent while the patient was breathing pure oxygen and this was done prior to recording. Time lag and drift were occasionally troublesome but could be mitigated with constant balance adjustment.

TABLE OF RESULTS

Case No.		Time in minutes										Immediate postoperative P_{CO_2} (mm Hg).	Weight (lb)	Predicted ventilation (l./min)	Percentage of predicted ventilation (mean)	Mean oxygen saturation (per cent)
		5	10	15	20	25	30	35	40	45	50					
1.	V.	5.1	5.9	5.1	5.6	5.0	5.1	6.7	6.1	5.4	—	48	153	5.8	95	96
	O.	100	98	98	97	96	98	100	98	98	—					
2.	V.	6.1	5.1	7.5	4.0	6.8	4.8	—	—	—	—	40.5	130	5.3	107	97
	O.	97	97	97	93.4	98.5	98	—	—	—	—					
3.	V.	4.5	4.3	5.4	6.5	5.4	5.9	6.7	—	—	—	42.2	126	5.2	104	96
	O.	96	95	99	96	96	94	96	—	—	—					
4.	V.	2.9	5.1	5.6	5.3	6.1	5.8	—	—	—	—	41	185	6.5	78.5	94
	O.	88	96	94	96	98	95	—	—	—	—					
5.	V.	3.6	4.7	4.7	4.8	5.8	3.9	4.5	3.3	—	—	45	149	5.7	77.2	93
	O.	92	94	98	94	95	93	96	88	—	—					
6.	V.	5.2	8.8	6.7	5.9	3.2	7.3	7.3	10.0	6.7	—	44	162	6.1	108	97
	O.	96	99	98	98	90	96	95	96	96	—					
7.	V.	5.6	4.6	6.3	6.6	5.6	7.0	5.1	—	—	—	39	134	5.4	107	97
	O.	96	95	98	98	95	98	94	—	—	—					
8.	V.	6.7	6.8	6.8	7.2	7.3	4.2	8.5	7.6	—	—	43	219	7.3	93.2	91
	O.	96	90	88	90	89	—	99	90	—	—					
9.	V.	4.4	6.6	6.4	7.9	10.5	6.7	7.3	—	—	—	46	172	6.3	112.7	96
	O.	97	94	95	97.5	98	94	95	—	—	—					
10.	V.	3.6	5.8	4.2	6.0	4.1	3.9	4.4	4.3	—	—	53	132	5.3	85	95.5
	O.	100	95	90	98	93	94	98	97	—	—					
11.	V.	4.7	2.8	5.9	6.7	7.5	6.2	—	—	—	—	60	154	5.9	96.5	98
	O.	97	—	98	98	99	97	—	—	—	—					
12.	V.	8.2	6.7	7.5	7.1	7.1	5.7	5.8	7.0	6.3	5.1	50	152	5.8	114	92
	O.	98	92	90	92	92	89	88	93	91	95					
13.	V.	5.6	6.5	3.9	5.2	6.0	6.5	—	—	—	—	43	170	6.25	88	94
	O.	94	97	88	99	96	94	—	—	—	—					
14.	V.	4.3	6.9	3.1	4.6	5.1	5.2	4.7	—	—	—	44	178	6.4	75	95
	O.	95.5	99	94	99	96	97	96	—	—	—					
15.	V.	7.5	5.9	7.2	4.6	5.2	6.2	4.5	—	—	—	37	152	5.8	100	95
	O.	96	95	98	95	96	98	95	—	—	—					
16.	V.	4.5	5.1	4.4	6.7	6.5	6.5	—	—	—	—	44	172	6.3	87.5	97
	O.	97.5	97	95	98	99	99	—	—	—	—					
17.	V.	6.2	7.2	7.0	7.1	6.1	6.1	5.9	—	—	—	62	147	5.7	114	96.5
	O.	96	95	97	96.5	97.5	98	96	—	—	—					
18.	V.	6.9	6.5	8.5	6.7	7.0	6.2	5.0	—	—	—	42	173	6.3	111	97
	O.	96.5	95	100	97	99	98	98	—	—	—					
													S.D. of mean		11.3	1.95

V.=Minute volume (l.). O.=Percentage oxygen saturation.

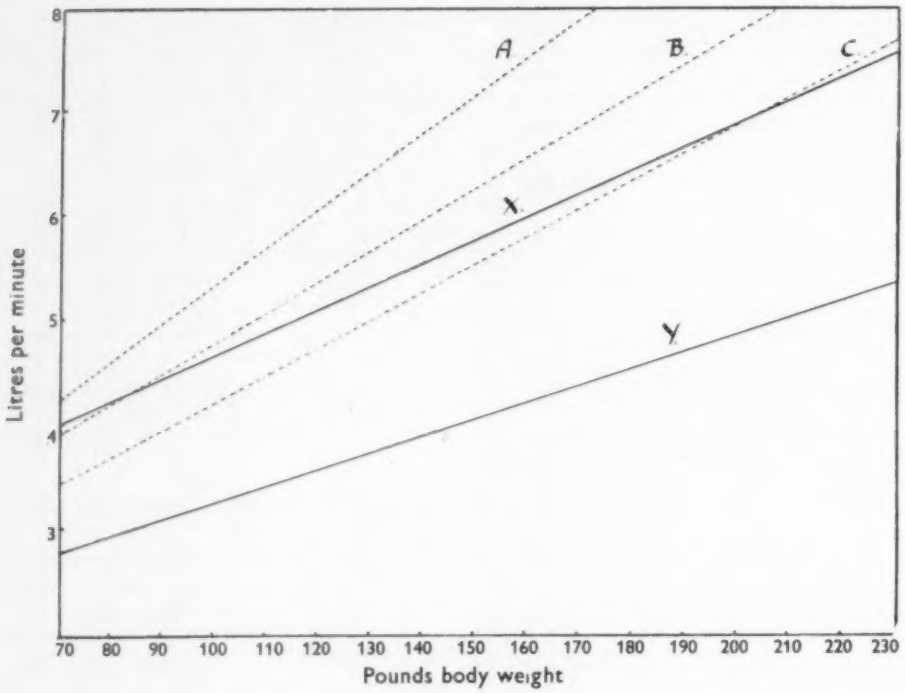

FIG. 1

Modification of the Radford Nomogram.
A, B and C are the total ventilations at 10, 15, and 20 respirations per minute respectively.
X is the predicted ventilation during anaesthesia (alveolar ventilation × 1.43).
Y is the alveolar ventilation (plotted between 12 and 18 respirations per minute).

RESULTS

These are set out in the table. Frank cyanosis was observed in two cases (8 and 11); certainly when saturation figures above 90 per cent were recorded the patients appeared quite satisfactory. Changes in the saturation figures did not always correspond with changes in ventilation, due to factors mentioned above concerning the oximeter but constant observation of the changing levels between recording times did demonstrate a fairly close relationship. A continuous record would be preferable. The mean of minute volumes does not, of course, imply adequate ventilation at all times but it is an indication of overall ventilation; similarly with the mean of saturation levels. Generally both ventilation and saturation were adequate. For reasons mentioned above the recorded relation between means was poor; the correlation coefficient using a derived formula for small series was less than statistically significant. The saturation curves are plotted in figure 2 where the general pattern can be seen. Figure 3 shows the ventilation range (percentage of predicted ventilation).

Carbon dioxide levels postoperatively were within acceptable limits. One figure of 60 mm was probably due to extubation spasm with a period of apnoea. Operating conditions were satisfactory and all patients were awake and in good condition on return to the ward.

DISCUSSION

The patients selected for this investigation were healthy men and had no depletion of blood

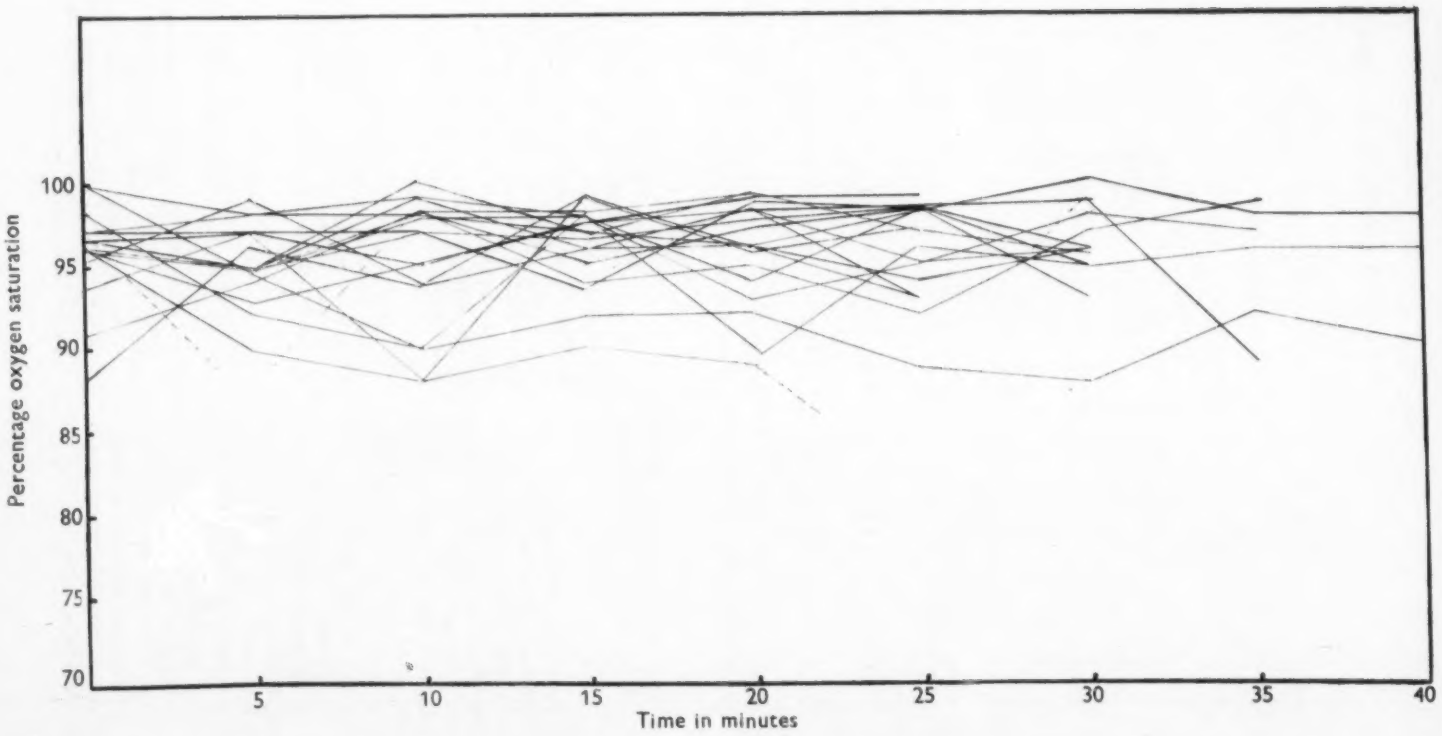

FIG. 2

Oxygen saturation levels of the eighteen patients plotted against time.

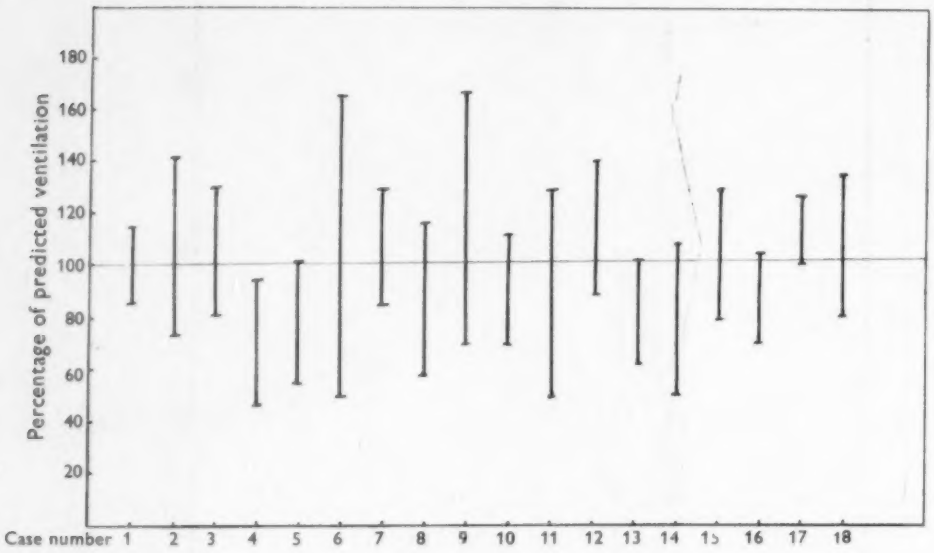

FIG. 3

The ventilation range (percentage of predicted ventilation) of each case.

volume. The use of air in cases of this type appears to be justifiable, particularly if ventilation is metered and assistance to respiration is applied from time to time.

While in this series the ventilation of the patients was left unaided for observation purposes, assistance on only a few occasions would have provided satisfactory ventilation throughout. With war casualties quite different conditions might be encountered and here the addition of small quantities of oxygen would probably be essential. With the machine described it is very easy both to assist respiration and to add small flow rates of oxygen. At a ventilation of 5 l./min the addition of 250 ml brings the oxygen percentage up to 26.

Although during anaesthesia with the use of conventional gases hypoventilation need not imply hypoxia, adequate ventilation is essential if air is substituted and with a ventilation meter any tendency towards inadequacy can be prevented before hypoxia occurs. There may be a place for this technique in routine anaesthesia but certainly where there is cylinder supply difficulty or shortage it might be of considerable value.

SUMMARY

Ventilation was measured in eighteen patients anaesthetized with air and the halothane-ether azeotrope. Minute volumes and oxygen saturation were mostly adequate and under normal conditions would have been entirely so with occasional assisted respiration. The technique is suggested for use under conditions of supply failure and other adverse conditions and possibly routinely.

ACKNOWLEDGMENTS

I am indebted to the surgeons in this hospital for their co-operation, to Corporal Technician P. J. Kelly for his assistance, and to the Director-General of Medical Services, Royal Air Force, for permission to publish.

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Brit. J. Anaesth. (1961), 33, 296

SOME FACTORS INFLUENCING THE INDUCTION CHARACTERISTICS OF METHOHEXITONE ANAESTHESIA

BY

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IN studies of the action of a fixed dose of methohexitone used for a standard operation, Dundee and Moore (1961a, b) and Moore and Dundee (1961a) found that the incidence of side effects occurring during the induction of anaesthesia varied with different forms of premedication. Since it was not certain how far these findings could be applied to everyday practice, an investigation of factors likely to influence the induction characteristics of the drug was carried out and is reported in this paper. It is essentially an analysis of the effects of three variable factors: the dosage, the percentage of solution, and the premedication.

All anaesthetics were administered personally by the authors to unselected patients aged 15 years and over, who conformed to the requirements of physical status classes 1 and 2 of the American Society of Anesthesiologists classification. A variety of anaesthetic techniques was used but observations were limited to the first few minutes after injection of the methohexitone. When a long acting muscle relaxant was required, an interval of about 2 minutes was allowed to elapse before its administration so that the action of the methohexitone alone could be observed.

A variety of premedicants was given to the 1,750 patients in this investigation and these have been grouped as follows:

(*a*) Atropine alone (usually 0.6 mg).
(*b*) Opiate-atropine. The opiate consisted of either pethidine 50–100 mg, morphine 10–15 mg or papaveretum 15–20 mg.
(*c*) Hyoscine alone (usually 0.4 mg).
(*d*) Opiate-hyoscine.
(*e*) Phenothiazine-atropine. Various phenothiazine derivatives were used including promethazine 10–50 mg, pecazine 25–50 mg, promazine 25–100 mg and perphenazine 5 mg.
(*f*) Opiate-phenothiazine-atropine. This consisted of a mixture of (*b*) and (*e*) above.

For obvious reasons groups (*e*) and (*f*) are of lesser clinical importance than the others. The anaesthetics were recorded on the special chart described by Dundee and Moore (1961a) and the main observations consisted in recording the incidence and severity of excitatory phenomena (tremor and abnormal spontaneous muscle movements), respiratory upset (cough, hiccough and laryngospasm), respiratory depression and hypotension. Each administration was graded according to a modification of the scheme employed by Dundee and Riding (1960). This will be described fully later.

RESULTS

Dosage.

When the data for the most commonly used premedicants (atropine, 450 cases; opiate-atropine, 600 cases) were analyzed a striking relationship was found between the incidence of excitatory phenomena and respiratory upset, and the induction dose of methohexitone (fig. 1). The increase in frequency of both these complications with dosage was less marked in the patients who received an opiate before induction.

As a consequence it can be seen that the incidence of grade 1 induction (complete absence of all complications) decreased with increasing dosage of methohexitone. Part of this increase can be attributed to the hypotension which may follow large induction doses of the barbiturate.

Percentage of solution used.

From the same group of patients the dosage range which contained most cases was selected

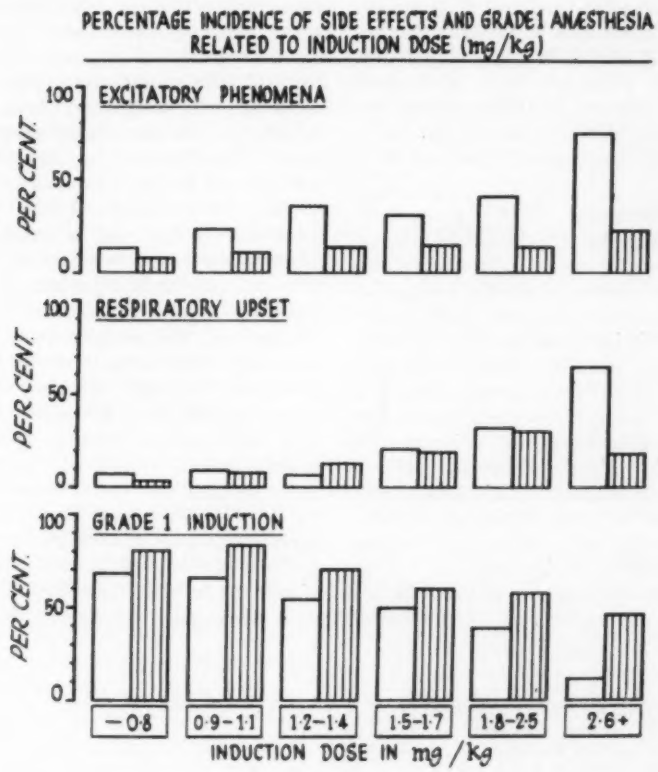

FIG. 1

Relationship between the induction dose of methohexitone (mg/kg) and the incidence of excitatory phenomena, respiratory upset and grade 1 induction.

Atropine premedication.

Opiate-atropine premedication.

TABLE I

Percentage incidence of complications following injection of 1.5–1.7 mg/kg methohexitone related to the percentage of solution injected.

Premedication	Per cent solution	Excitatory phenomena			Respiratory upset
		Tremor	Muscle movement	Nil	
Atropine	1	14	24	70	24
	2	22	18	68	18
Opiate-atropine	1	9	10	84	17
	2	7	0	88	21

(1.5–1.7 mg/kg) and the incidence of complications following the use of a 1 per cent solution was compared with that following a 2 per cent solution (table I). Although there were some minor differences between the effects of the two concentrations, particularly in the atropine series, these do not reach the accepted 5 per cent level of significance.

Pre-anaesthetic medication.

Before comparing the effects of the various premedications it was necessary, in view of the above findings, to establish that the average induction dose of methohexitone was fairly similar in each series. This is shown in table II, which also shows the physical characteristics of each group of patients. Apart from a much lower proportion of females in the group premedicated with an opiate-phenothiazine-atropine mixture, the six series are fairly closely comparable and, in view of the findings of Dundee and Riding (1960) that there was no sex variation in the incidence of complications with some intravenous barbiturates, this difference can be ignored.

Table III shows the incidence of the complications following induction of methohexitone anaesthesia with the six forms of premedication used in this study. It can be seen that the presence of an opiate reduced the incidence of tremors and involuntary muscle movements following methohexitone as compared with the effect of the same premedication without an opiate. The frequency of respiratory upset was also reduced by the opiate but not to the same extent as the excitatory phenomena. Against these beneficial effects it can be seen that an opiate increased the incidence of marked respiratory depression, particularly when combined with hyoscine.

Compared with atropine, hyoscine significantly increased the incidence of involuntary muscle movements but had little effect on the frequency of tremor. The same differences were found, but to a lesser extent, between opiate-atropine and opiate-hyoscine. It was surprising to find that the pre-anaesthetic use of hyoscine was followed by a significantly lower incidence of respiratory upset than atropine ($\chi^2 = 29.42$; $P < 0.001$). This fact was also noted when these drugs were combined with an opiate ($\chi^2 = 5.71$; $P < 0.02$).

In the opiate-hyoscine group, the induction of an-

TABLE II

Details of the physical characteristics of the patients and the induction doses of methohexitone

Pre-anaesthetic medication	No. of patients	Per cent females	Age (years)		Weight (kg)		Induction dose (mg/kg)	
			Average	Range	Average	Range	Average	Range
Atropine	450	60	41.5 ± 0.80	15–87	60.3 ± 1.99	25–98	1.47 ± 0.026	0.39–3.24
Opiate-atropine	600	65	39.4 ± 0.63	15–78	61.7 ± 0.49	30–96	1.55 ± 0.022	0.52–3.52
Hyoscine	150	65	42.8 ± 1.19	15–79	62.8 ± 1.88	31–98	1.37 ± 0.029	0.79–3.29
Opiate-hyoscine	150	70	37.6 ± 1.05	16–69	61.4 ± 0.29	23–93	1.37 ± 0.025	0.62–3.31
Phenothiazine-atropine	200	66	36.0 ± 1.01	15–70	59.4 ± 0.46	40–100	1.44 ± 0.030	0.57–3.10
Opiate-phenothiazine-atropine	200	53	30.0 ± 0.91	15–77	60.0 ± 0.99	42–84	1.51 ± 0.028	0.91–2.73

TABLE III

Percentage incidence of induction characteristics with six different forms of premedication in patients described in table II.

Pre-anaesthetic medication	Excitatory phenomena			Respiratory upset	Marked respiratory depression
	Tremor	Muscle movements	Nil		
Atropine	24	18	66	19	3
Opiate-atropine	9	6	87	15	8
Hyoscine	26	47	42	11	2
Opiate-hyoscine	11	16	78	8	15
Phenothiazine-atropine	32	42	48	28	2
Opiate-phenothiazine-atropine	17	15	74	10	3

aesthesia was associated with a significantly higher incidence of marked respiratory depression than in the opiate-atropine series ($\chi^2=6.20$; $P<0.02$). Despite the arbitrary classification of "marked respiratory depression" the authors feel that this difference is of clinical significance. In support of this is the fact that the average induction dose of methohexitone was lower than in the opiate-atropine group ($t=5.29$; $P<0.001$).

Too much importance must not be attached to the results in the phenothiazine-atropine and opiate-phenothiazine-atropine series because of the variety of phenothiazine derivatives used. However, it can be seen that, compared with atropine alone, the phenothiazine compounds used in this study resulted in an increase in involuntary muscle movements and respiratory upset following injection of methohexitone. They did not appear to enhance the respiratory depressant action of the barbiturate.

In order to assess the clinical significance of the effects of the various premedications studied, the grades of induction described by Dundee and Riding (1960) were modified as follows:

(1) Smooth uncomplicated induction.

(2A) Slight upset not interfering with the conduct of anaesthesia.

(2B) Slight upset during the induction period, which interfered with the course of anaesthesia but was not as marked as in grade 3.

(3) Serious difficulties making surgery impossible or placing the patient's life in jeopardy (including severe prolonged hypotension).

It will be seen that this is similar to the original grading except that grade 2 is subdivided into two classes, 2A being of no clinical significance and 2B being of clinical significance. The percentage distribution of induction grades with the six forms of premedication under study is shown in table IV.

This table shows that both hyoscine and the phenothiazine derivatives used in this study were unsatisfactory premedicant drugs for use before methohexitone. Best results were obtained with an opiate (pethidine, morphine or papaveretum) combined with atropine but when atropine was replaced by hyoscine the overall results were less satisfactory.

TABLE IV

Percentage incidence of induction grades with the six forms of premedication under study.

Pre-anaesthetic medication	Induction grade			
	1	2A	2B	3
Atropine	54	34	7	5
Opiate-atropine	68	25	5	2
Hyoscine	37	28	27	8
Opiate-hyoscine	57	23	13	7
Phenothiazine-atropine	37	23	16	24
Opiate-phenothiazine-atropine	61	28	6	5

A statistical comparison of the distributions of the induction grades with various premedications can be made using the "ridit" method of analysis (Bross, 1958; Bellville, Bross and Howland, 1959a, b, 1960). Since, as far as the authors are aware, this technique has not been employed in British anaesthetic literature, it is proposed to summarize briefly the principles of the method.

Cases are assigned to a particular category on purely qualitative clinical grounds. A simple average value of scores in a series is of some value but is meaningless as regards the ability to compare it statistically with the mean value in another series. By using the ridit transformation these arbitrary numbers and classifications acquire a specific meaning in terms of probabilities. In ridit analysis a specified series of patients is chosen as the reference set ("identified distribution") and all comparisons are automatically made with this set (Relative to Identified Distribution—hence origin of term RIDIT). By virtue of the method of calculation, the average ridit for the control series will be 0.5.

The results of ridit analysis are usually presented graphically, showing the mean value and 95 per cent confidence limits. In this paper (fig. 2) the 99 per cent confidence limits of the mean are given.

When applied to the grades of induction a ridit higher than the control indicates that the variable factor (premedication) has an overall deleterious effect on the induction of anaesthesia (fig. 2). Whether this reaches the accepted levels of significance depends on whether the confidence limits of the control and "test" group overlap.

In figure 2 it can be seen that opiate-atropine premedication resulted in a significantly smoother induction of anaesthesia with methohexitone than premedication with atropine alone. On the other hand, hyoscine had an adverse effect on the

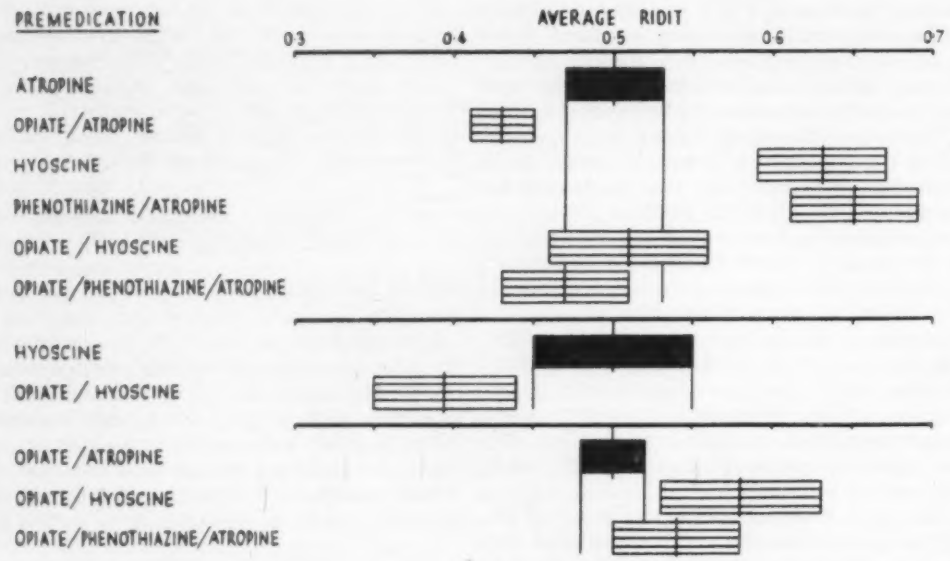

FIG. 2

Comparison of the induction grades of methohexitone anaesthesia with different premedications using the ridit transformation method of analysis.

Control group (identified distribution). Series compared with control.

Upright lines indicate mean ridit and blocks indicate 99 per cent confidence levels.

induction and this also applied to the mixed phenothiazine-atropine series. The addition of an opiate to hyoscine significantly reduced the incidence of complications during the induction of anaesthesia and the results obtained with this combination were similar to those with atropine alone.

Premedication with opiate-hyoscine was not as satisfactory, as regards the course of the subsequent anaesthesia, as was opiate-atropine. A similar, but less marked effect, was observed when a phenothiazine derivative was added but, for reasons given above, too much attention must not be given to this finding.

DISCUSSION

The relationship between the incidence of excitatory phenomena and the dosage of methohexitone is similar to that described by Dundee, Barron and King (1960) for 1-methyl 5-ethyl, 5′-methyl propyl thiobarbiturate (B.137). Both these compounds have a methyl group in the N_1 position and this may well be a property of all methylated barbiturates and thiobarbiturates. It is worth noting that a large number of methylated thiobarbiturates have been subjected to clinical trial by Stoelting (1953), Stoelting and Graf (1954) and by Barron and Dundee (1961b), but they were abandoned because of the high incidence of induction complications. Had these studies been continued a similar relationship between dose and complication incidence might have been found. In contradistinction to B.137, it was possible to demonstrate a relationship between the frequency of respiratory upset and the dosage with methohexitone, but this complication was not a feature of anaesthesia with the methylated thiobarbiturate.

The effects of the various premedicants shown in table III are qualitatively similar to those re-

TABLE V

A summary of published data on the incidence of induction complications following 1.6 mg/kg methohexitone used for a standard operation.

Pre-anaesthetic medication	Total excitatory phenomena (%)	Respiratory upset (%)	Reference
Atropine 0.6 mg	34	30	Dundee and Moore (1961a)
Pethidine 100 mg; atropine 0.6 mg	8	12	Dundee and Moore (1961a)
Hyoscine 0.4 mg	54	14	Dundee and Moore (1961b)
Pethidine 100 mg; hyoscine 0.4 mg	17	6	Dundee and Moore (1961b)
Promethazine 50 mg; atropine 0.6 mg	81	41	Moore and Dundee (1961a)
Pethidine 100 mg; promethazine 50 mg; atropine 0.6 mg	35	14	Moore and Dundee (1961a)

ported in the literature when a fixed dose (1.6 mg/kg) of the drug was given for a standard operation (table V). This confirms the validity of observations made on an unselected group of patients and justifies an attempt to offer an explanation for the results.

Dundee and Moore (1961b) observed a relationship between the incidence of excitatory phenomena following methohexitone and the analgesic action of the premedication. Drugs which increased sensitivity to somatic pain caused a high incidence of this complication, whereas pethidine lowered the incidence. The present report confirms these findings in patients undergoing general surgery.

It is of interest to note that the incidence of excitatory phenomena with promethazine 50 mg (table V) was higher than that found with the mixed phenothiazine derivatives in this study (table III). Moore and Dundee (1961b) observed that promethazine 50 mg had a very marked anti-analgesic action which was not shared by promazine or perphenazine, which drugs were also used in this study. These studies have since been carried a stage further and it has been possible to demonstrate a relationship between the analgesic action of nine different phenothiazine derivatives and the incidence of excitatory phenomena with 1.6 mg/kg methohexitone, when they were used as premedication. A report on this investigation is in preparation.

Although only introduced into clinical practice within the past few months, methohexitone has been subjected to extensive clinical trials and detailed reports of many thousands of administrations are recorded in the literature. It is remarkable that none of these reports (excepting those listed in table V) has mentioned the relationship demonstrated here between dosage or premedication and the incidence of complications following induction. However, the importance of these factors is shown by a recent review of the literature on methohexitone in which Barron and Dundee (1961a) noted variations from zero to almost 50 per cent in the frequency of side effects reported by different workers. It is hoped that this publication will clarify some of the causes for these discrepancies.

ACKNOWLEDGMENTS

We are indebted to Eli Lilly and Company for generous supplies of methohexitone (Brietal sodium) and to Mr. G. A. Smyth for the preparation of the illustrations. We wish to acknowledge advice on the use of the ridit analysis technique from Drs. E. A. Cheeseman, I. D. J. Bross and J. W. Bellville.

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CORRESPONDENCE

HYPERVENTILATION AND METABOLIC ACIDOSIS

Sir,—In the article by Robinson (1961), we were surprised to find ourselves credited with the suggestion that "respiratory alkalosis produced by hyperventilation during anaesthesia is completely controlled by the production of a metabolic acidosis".

The suggestion was derived not from a paper by ourselves but from remarks during discussion at the "Symposium on pH and Blood Gas Measurement" (1959). Reference to the transcript of the discussion will reveal that no such suggestion was made. One of us (M.H.) reported that "in three patients who were under controlled respiration . . . and had P_{CO_2}s of about 28 millimetres, the metabolic acidosis was sufficient to entirely compensate the respiratory alkalosis".

We feel strongly that the freedom of discussion at a scientific meeting will be greatly curtailed if the reporting of findings in three patients is interpreted by others (not present at the symposium) as a "suggestion" of apparently universal application.

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Middlesex Hospital, London, W.1
J. F. NUNN
Royal College of Surgeons of England

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Symposium on pH and Blood Gas Measurement (1959), edited by R. F. Woolmer, p. 79. London: Churchill.

This letter was shown to Dr. J. S. Robinson who submitted the following reply:

Sir,—This criticism seems a trifle surprising. The discussion at the symposium was obviously intended to reach a wider public. The fact that the proceedings of the symposium were not published simply for private circulation must imply that it was intended that it should be read by those "not present at the symposium". Presumably the signatories were given the opportunity of eliminating or modifying equivocal material before publication. Certainly, this passage seems to have been misconstrued frequently: it has often been quoted to me as evidence contraindicating the use of hyperventilation during anaesthesia.

JOHN S. ROBINSON
Liverpool

A. C. KING LTD

Sir,—May I be allowed to add a postscript to my letter under the above heading printed in your issue of January last (*Brit. J. Anaesth.*, **33**, 39).

I have been assured by the British Oxygen Company, through the kindness of Mr. F. W. B. Kittel, that the name of A. C. King, which still appears associated with that of the parent company on the facia over the showroom in London, will remain so associated for the immediate future.

It is over 20 years since A. C. King Ltd. became part of the British Oxygen Company, and those who are able to visit the showroom will realize that the same friendly welcome and service is extended quite unaffected by these changes, which, I believe, merely indicate that the present company now shows openly that it accepts full responsibility for the maintenance of the services provided for so long under the name of A. C. King.

It is most reassuring to know that a large organization can, with us, take pride in an example of individual service and I believe that this happy state of affairs will remain for many long years to come.

T. DINSDALE
Manchester

Brit. J. Anaesth. (1961), **33**, 303

MANAGEMENT OF ANAESTHESIA DURING PROFOUND HYPOTHERMIA

BY

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MANY centres of cardiac surgery are now using deep hypothermia with extracorporeal circulation. For this, two techniques are available; a pump-oxygenator may be used, with a heat exchanger (Ross, 1960), or alternatively the patient's lungs may be used to oxygenate the blood, which is then circulated through the pulmonary and systemic vessels by means of two extracorporeal pumps (Drew and Anderson, 1959; Drew, Keen and Benazon, 1959). Working in the Nuffield Department of Surgery in Oxford, we have been using a Gibbon pump-oxygenator and the purpose of this article is to give an account of the procedure that we adopt, with special emphasis on the practical lessons we have learned in connection with anaesthetic management.

THE ADVANTAGES OF DEEP HYPOTHERMIA AND CIRCULATORY ARREST

The principle of lowering the body temperature in order to reduce tissue oxygen requirements is well established. Clinically, the conventional limit to hypothermia has always been 28–29°C, because of the danger of ventricular fibrillation, but if an extracorporeal pumping system is available to maintain the circulation, temporary ventricular fibrillation no longer matters and there is no theoretical limit to the degree of hypothermia which may be induced. If a heat exchanger is incorporated in the pumping circuit, body temperature may be lowered more rapidly and predictably than by any other means.

With profound hypothermia many of the disadvantages of perfusion at normal temperature can be avoided. For example, the performance of exacting operations within the heart is greatly facilitated by cardiac arrest with a completely dry field; the heart stops during profound hypothermia, and this is preferable to the use of drugs to produce cardiac arrest since it is now believed that these may cause myocardial damage (Greenberg, Edmunds and Brown, 1960; Kusunoki et al., 1960). At a temperature of 10–13°C perfusion may be discontinued completely for at least 1 hour without apparent ill effect; once the heart has been emptied of blood the surgeon's view is then unimpeded and if necessary cannulae may be removed from the heart and great vessels. A sucker is not needed to return blood from the coronary sinus to the pump-oxygenator; with continuous normothermic perfusion this has always been a problem because, apart from interfering with the surgeon's view, such suckers are responsible for a great deal of haemolysis.

PERFUSION

Much of the early work on extracorporeal circulation was carried out with low rates of perfusion (Sealy, Brown and Young, 1958). This was to some extent unavoidable, because oxygenators large enough to provide high perfusion rates to adult patients are difficult and expensive to manufacture and require large quantities of blood. Nevertheless, experience over the years has shown that although perfusion at low rates of flow may be adequate to maintain life during the period of time required for an intracardiac operation, it is far from ideal from the point of view of tissue metabolism in general: considerable metabolic acidosis results from this type of perfusion and the majority of workers now use pump oxygenators capable of delivering high flow rates to even the largest patients.

An advantage that has been claimed for deep hypothermia is that, because tissue oxygen requirements are reduced, a lower perfusion rate becomes feasible and thus a smaller oxygenator and a smaller volume of blood can be used. This argu-

ment may not be entirely sound, however, since perfusion rate probably makes a considerable difference to the partial pressure of oxygen in the tissues (see below). Also, if a low rate of perfusion is used during cooling, intense vasoconstriction develops and a severe metabolic acidosis still occurs. For these reasons, we now believe that high rates of perfusion are advisable even with the hypothermic technique: with a high flow of blood through the patient's tissues, vasoconstriction is more easily avoided and even after prolonged circulatory arrest metabolic acidosis is slight (Pierucci, Haupt and Templeton, 1960).

Technically, if a well-tried pump-oxygenator and an efficient heat exchanger are available, the problems of perfusion at low temperatures are not greatly different from those of normothermic perfusion. Once a film of blood has been created on the oxygenating screens of the Gibbon machine, pumping must be continuous or else the blood film will break: thus, blood continues to flow round the pump-oxygenator circuit even during the period of complete circulatory arrest for the patient. The practical consequence of this is that the total length of time during which blood is subjected to the effect of the extracorporeal pumps is considerably prolonged; allowing for the period of cooling, the period of circulatory arrest and the period of rewarming, this time may be anything up to 3 hours as compared to an average of about 45 to 60 minutes with normothermic perfusion. However, most extracorporeal pumps in current use cause only very slight amounts of haemolysis even after these longer periods of time.

OXYGEN TRANSPORT

A continuous flow of 10 l. of oxygen and 300 ml of carbon dioxide per minute is passed through the oxygenator, so that the contained blood is subjected to a high partial pressure of oxygen. The efficiency of an oxygenator varies in different circumstances but the work of Kirklin, Theye and Patrick (1958) suggests that in the Gibbon oxygenator a blood oxygen tension of 100 to 250 mm Hg is obtained after one passage across the screens, during normothermic perfusion. In practice, the oxygen saturation of the blood leaving the oxygenator varies between 96 and 100 per cent.

When hypothermia is induced, certain additional factors must be taken into consideration. According to Mustafa Oz et al. (1960), with a temperature drop from 38°C to 10°C the viscosity of the blood increases by 55 per cent. This means that unless the extracorporeal pumps are specially calibrated for low temperature work, the actual perfusion flow rate received by the patient will be considerably less than that indicated on the machine gauge. A further problem concerns the solubility of oxygen in blood: this increases as the blood temperature falls, so that if the blood is fully oxygenated at a temperature below that of the body there is a danger that micro-emboli will form. In practice, the temperature of the blood must be reduced, by the heat exchanger, to considerably below that of the patient in order to facilitate cooling; the temperature of the perfused blood, which we now measure by means of a thermocouple incorporated in the circuit, may be as low as 4°C. The danger of micro-emboli is avoided by oxygenating the blood at or above the temperature of the patient and then cooling it by interposing the heat exchanger between the oxygenator and the arterial line.

We are indebted to Dr. R. Marshall for the following theoretical considerations concerning the influence of perfusion flow rate and arterial oxygen saturation on tissue oxygen tension:

Consider the case of an adult patient at a temperature of 20°C. Assume that the blood has an oxygen capacity of 16 vol. per cent, and assume that the body oxygen uptake is 50 ml./min.

With a perfusion rate of 3 l./min.

The patient must extract 50 ml oxygen from each 3,000 ml blood, i.e. 5/3 ml oxygen from each 100 ml blood.

$\therefore$ A–V oxygen difference = 1.7 ml per cent.

Assuming a blood oxygen tension of 200 mm Hg (arterial), then

Haemoglobin saturation will be 100 per cent.
Dissolved oxygen (at 20°C) will be 0.9 vol per cent (Bartels and Opitz, 1958).

$\therefore$ Venous oxygen saturation

$$= \frac{16.9-1.7}{16.0} = 95.0 \text{ per cent.}$$

At 37°C this would represent a venous oxygen tension of 80 mm Hg, but at 20°C the following values would obtain (Severinghaus, 1958):

At pH 7.4 venous Po_2 = 38 mm Hg
At pH 7.0 venous Po_2 = 56 mm Hg
At pH 7.6 venous Po_2 = 30 mm Hg

If the oxygenator performance is such that only 95 per cent arterial saturation is obtained, then

arterial oxygen tension will be 37.5 mm Hg
dissolved oxygen tension will be 0.16 vol. per cent
} at 20°C.

Venous oxygen saturation

$$= \frac{15.36 - 1.6}{16.0} = 86.3 \text{ per cent}$$

thus, at pH 7.4, venous Po_2 = 25 mm Hg
at pH 7.0, venous Po_2 = 37 mm Hg
at pH 7.6, venous Po_2 = 20 mm Hg

With a perfusion rate of 1 l./min.

A–V oxygen difference = 5.0 ml per cent.

Assuming a blood oxygen tension of 200 mm Hg (arterial),

venous oxygen saturation

$$= \frac{16.9 - 5.0}{16.0} = 74.4 \text{ per cent.}$$

at 20°C, at pH 7.4, venous Po_2 = 19 mm Hg
at pH 7.0, venous Po_2 = 28 mm Hg
at pH 7.6, venous Po_2 = 15 mm Hg

If the oxygenator performance is such that only 95 per cent arterial saturation is obtained,

at pH 7.4, venous Po_2 = 16 mm Hg
at pH 7.0, venous Po_2 = 23 mm Hg
at pH 7.6, venous Po_2 = 13 mm Hg

The important points to be noted from the above calculations are firstly, that although venous oxygen saturations may be high during hypothermic perfusion, the actual oxygen tension in this venous blood is remarkably low. Furthermore, a reduction of the perfusion flow rate from 3 l./min to 1 l./min would be expected to reduce the venous oxygen tension by 100 per cent for any given pH. It would appear that the tendency for blood pH to fall when low perfusion rates are employed might offer some measure of protection to the tissues since their oxygen tension would be considerably higher than with a pH in the normal range. Nevertheless, the advantage of a higher perfusion rate is clear.

TEMPERATURE

A difficulty common to all forms of hypothermia is vasoconstriction in response to cooling, with consequent "gradients" of temperature between different parts of the body. When this occurs, it is meaningless to speak of the patient's temperature, since the temperature of each organ may be different; for example, the reading of an oesophageal thermometer may give a completely unrealistic impression of the temperature of the brain. This difficulty has given rise to much heated argument as to the "best" site for temperature measurement during hypothermia.

When inducing hypothermia by means of a pump oxygenator, vasoconstriction may be prevented by using high perfusion rates and by reducing the temperature of the perfused blood slowly rather than suddenly: it is most important to ensure that the blood is at body temperature when perfusion begins, otherwise the sudden introduction of cool blood will invariably cause the vascular bed to constrict at the outset. If significant temperature gradients are avoided in this way, a single reliable thermometer placed in the upper oesophagus is quite adequate.

Cooling to 10°C usually takes place in 30 to 40 minutes. During circulatory arrest for about 1 hour, in an air-conditioned operating theatre, the patient's temperature may rise by 2 to 3°C. Rewarming can be accomplished as quickly as possible and the temperature should be taken up to at least 36°C before perfusion is discontinued. Indeed, it is advisable to maintain perfusion for 10 to 15 minutes after normal temperature has been restored, as otherwise a considerable fall in body temperature may occur during the concluding stages of the operation. This is particularly likely if large volumes of stored blood have to be transfused: it is disturbing if cardiac arrhythmias are present or if atropine and neostigmine have to be given.

ANAESTHESIA

Most of the common inhalation agents have been advocated for extracorporeal circulation work (Mendelsohn et al., 1957; Patrick, Theye and Moffitt, 1957; Telford and Keats, 1957; Dawson, Theye and Kirklin, 1960), and there is probably little to choose as long as the general principles of minimum dosage and efficient pulmonary ventilation are observed (Smith and Engineer, 1960). Facilities must always be available for aspirating secretions from the trachea and bronchi and at last one absolutely certain route for the intravenous administration of fluids and drugs must be established. Some workers have attempted to avoid the necessity for using atropine and neostigmine at the conclusion of the operation, in case a heart block or other rhythm disturbance should have resulted from the operative repair. While it is inadvisable to give these drugs to a hypothermic patient, there seems in practice to be no disadvantage in using them when the

body temperature has returned to normal: if their effect on the heart rate is particularly feared, they may be "titrated" against each other as described by Gray and Riding (1957). Hypothermia frees the anaesthetist from the responsibility of maintaining oxygenation and unconsciousness during perfusion and allows him to concentrate on assessing the adequacy of perfusion and on the problem of blood volume.

During hypothermia, halothane has been used to maintain vasodilatation (Campkin and Inglis, 1958; Vanderwater et al., 1958; Conn, Allan and Junkin, 1959). The same agent has been employed for extracorporeal circulation cases (Dawson, Theye and Kirklin, 1960), and the resulting vasodilatation enables high perfusion flows to be maintained (Bull, A., personal communication 1960). We have also used halothane in a few cases and as an alternative we have been impressed by the efficacy of trimetaphan injected intravenously at the beginning of perfusion.

During the period of extracorporeal circulation, when the normal pulmonary blood flow is in abeyance, it has been advocated that the lungs should remain slightly distended in order to prevent alveolar collapse (Patrick, Theye and Moffitt, 1957). Some workers have suspected that 100 per cent oxygen may have adverse effects on the respiratory epithelium when the pulmonary circulation is arrested, and the use of helium-oxygen mixtures, or air, has been recommended (Cleland et al., 1958). We have often allowed the lungs to collapse during perfusion; we have not encountered any difficulty in re-inflating them, and no postoperative pulmonary complications have resulted.

PROCEDURE

Before anaesthesia.

Babies are premedicated with atropine alone. Children are premedicated with a rapidly acting rectal thiopentone suspension (Abbott) and atropine. These children have often been subjected to numerous pre-operative investigations, many of which involve anaesthesia, and they are frequently aware of the gravity of the ensuing operation. Thus, apprehension is to be expected, and we make every effort to ensure that they are asleep on arrival in the anaesthetic room. Every child is under the continuous supervision of a doctor from the time that rectal thiopentone is given. Adults are premedicated with pethidine and hyoscine.

The patient is brought to the operating theatre in his bed and he and the bed are weighed together on a bed weighing machine.

Induction of anaesthesia.

In babies, the larynx is sprayed with not more than 0.5 ml of 4 per cent lignocaine and a flexometallic or Oxford endotracheal tube is passed. An oesophageal thermocouple is inserted and a small pack is placed gently in the pharynx: this holds both the thermometer and endotracheal tube in position. Respiration is then controlled using equal volumes of nitrous oxide and oxygen, small doses of d-tubocurarine being given as necessary. A small reservoir bag is used, with a high flow of fresh gases, the arrangement being similar to that described by Rees (1959), except that expired gases are voided through the open limb of a Y-shaped endotracheal connector which is intermittently occluded with the finger (Macintosh, 1955; Parkhouse, 1960).

In children, anaesthesia is induced with an oxygen and cyclopropane or oxygen and halothane mixture, which usually suffices for intubation. For adults a sleep dose of thiopentone is used and intubation is performed under the influence of a muscle relaxant. In both children and adults, anaesthesia is maintained with nitrous oxide and oxygen mixtures with or without the addition of small quantities of halothane, and d-tubocurarine chloride. The patient may be permitted to breathe spontaneously until the operation begins, and this frees the anaesthetist's hands for such duties as setting up of transfusions.

Preparation for perfusion.

When the patient is anaesthetized, he is placed supine on the operating table, with his arms at his sides. E.c.g. and e.e.g. leads are attached, the oesophageal thermocouple is inserted and a cannula is put into a convenient vein in the forearm. This cannula is connected by a length of drip tubing to a three-way tap which remains by the patient's head and provides a convenient route for injections; beyond the tap an additional length of drip tubing leads to the drip chamber and transfusion bottle. In babies a length of polythene tubing is inserted into a suitable vein by cut-down.

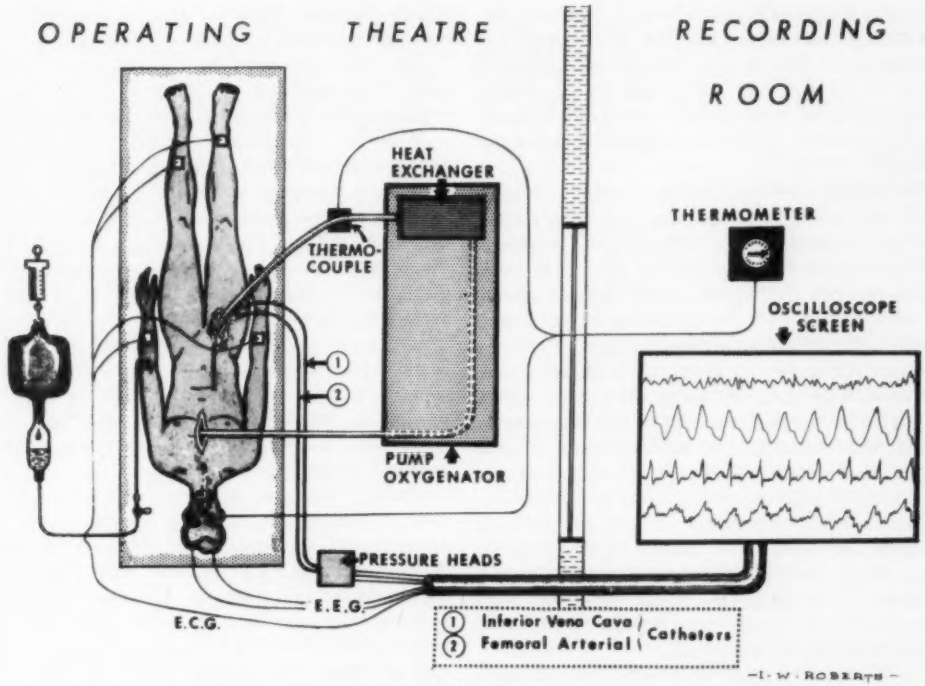

FIG. 1

Diagram illustrating arrangement of patient and monitoring equipment during profound hypothermia with extracorporeal circulation. Note spring balance for measuring the amount of blood given from plastic bags.

After preparation of the skin the chest and both groins remain exposed. In children and adults the right femoral artery is isolated ready for perfusion. In babies, whose vessels are small, both femoral arteries are isolated so that later two cannulae may be inserted to ensure adequate flow rates. A catheter is inserted through the left saphenous vein, at the groin, into the inferior vena cava and connected to a pressure recording head. This venous pressure, together with the e.c.g. and e.e.g are displayed on an oscillograph screen in the recording room adjacent to the theatre (fig. 1). This screen is clearly visible to the anaesthetist throughout the operation through an intervening glass panel.

The surgeon exposes the heart through a median sternotomy, and heparin is administered intravenously in a dose of 3 mg/kg body weight. After allowing 1½ minutes for the heparin to become effective, cannulae are placed in the femoral artery and the right atrium and these are connected to the pump-oxygenator. A check is made on blood loss at this stage, to ensure that replacement is adequate before perfusion begins.

During perfusion.

Extracorporeal circulation begins at 37°C, care being taken to ensure that the blood in the pump-oxygenator is at this temperature. The perfusion flow rate is calculated on the basis of 2.3 l./sq.m/min, this being the accepted "high flow" requirement. When this flow is given from the outset, with blood at body temperature, vasoconstriction can usually be avoided. If the flow rate tends to fall and signs of vasoconstriction appear a single injection of 25 to 50 mg of trimetaphan is given intravenously. By maintaining vasodilatation, and by adding blood from

the pump-oxygenator reservoir to compensate for the increase in vascular capacity due to paralysis of vasomotor tone at low temperature (Mustafa Oz et al., 1960), the calculated flow is nearly always exceeded even during hypothermia. Cooling begins when the maximum flow rate has been attained.

Ventricular fibrillation often occurs between 20°C and 27°C, although the rhythm may not alter until asystole occurs at about 20°C. At about 10°C the arterial line is clamped, the venae cavae are snared and the heart is sucked dry. The heart is then opened and the operation is performed during a period of complete circulatory arrest.

When the intracardiac operation is completed, perfusion recommences, using cold blood which is gradually warmed by raising the temperature of the heat exchanger to 42°C. The heart soon begins to contract and, if the ventricle is fibrillating, defibrillation is carried out at 28–29°C.

At 35–36°C the pump output is gradually lowered and the heart is allowed to take over for itself. When it is beating strongly and the arterial pressure is adequate, by which time the body temperature has usually been normal for 10 to 15 minutes, perfusion is stopped.

At the beginning of perfusion, anaesthesia is very light; minimum doses of drugs are used and intravenous analgesics are avoided since hypothermia delays their metabolism and excretion. When the patient's temperature has fallen below 28°C, no further anaesthetic is required. Gentle inflation of the lungs with oxygen is maintained until ventricular fibrillation or asystole occurs: this continued inflation tends to reduce the incidence of "bucking". The lungs are then left to collapse and the gas flow is turned off. When warming begins the lungs are again gently inflated to ensure that there will be no areas of atelectasis at the time perfusion is discontinued. Only oxygen is administered until movements of the patient make it necessary to add nitrous oxide.

After perfusion.

The residual effects of heparin are neutralized by the intravenous injection of Polybrene. Initially this drug is given in the same dosage (in mg) as the original quantity of heparin. A blood sample is then withdrawn and a heparin titration is carried out in the haematology laboratory: if this test reveals that some heparin remains un-neutralized, a further injection of Polybrene is given.

The perfusion cannulae are removed, haemostasis is secured and the chest is closed with a drainage tube connected to a suction bottle.

Many of our patients receive digitalis preoperatively, and after perfusion a rapidly acting digitalis preparation is frequently administered: for this purpose intravenous Cedilanid (Lanatoside C) is injected intravenously in small divided doses. Also, 50 to 100 mg of hydrocortisone are often given intravenously, firstly to safeguard against the development of an adrenal exhaustion syndrome, which has been described under profound hypothermia, and secondly because cortisone is known to restore the bleeding time to normal in cases in which it is prolonged preoperatively without discoverable cause (Sharp, personal communication, 1961).

During closure of the superficial layers of the wound spontaneous breathing recommences, and atropine and neostigmine are given as necessary. A bronchoscopy is performed after removal of the endotracheal tube, in case any secretions require to be aspirated from the bronchial tree; a radiograph of the chest is then taken before the patient leaves the operating theatre. When the patient's condition is satisfactory, he is transferred to his bed and reweighed. He is then returned to the ward with a blood drip running and the femoral venous catheter still in place. The venous pressure and e.c.g. are continuously recorded on an oscillograph screen during the early postoperative period.

MONITORING

In common with many other workers, we are convinced of the paramount importance of clinical observation of the patient. The e.e.g., e.c.g., and other measurements all have their place as supplementary indications of progress but they can never give as much information as careful study of the patient as a whole. It is important to note the skin colour, the arteriocapillary refill time and the appearance and behaviour of the heart and venae cavae: all of these give a good indication of the adequacy of perfusion and oxygenation. Inspection of the retinal vessels is easy when the pupils are widely dilated (as they are when trimetaphan is given) and the condition of these vessels gives some indication of the state of cere-

bral blood flow (Gerbode, Osborn and Johnston, 1960). Of the ancillary methods of monitoring, the most useful are the blood pressure, the central venous pressure, and the perfusion flow rate which is read from a precalibrated dial on the machine.

Blood pressure.

In one of our cases an extensive deep venous thrombosis occurred in the forearm following use of a sphygmomanometer cuff. Since this incident we have not used a cuff during profound hypothermia with circulatory arrest. During perfusion, pressure in the tubing between the arterial pump and the femoral artery (the arterial line) is measured and a table is available showing the pressure drop across arterial cannulae of various diameters at different flow rates: the mean arterial pressure in the patient's body may thus be determined by subtraction. This mean pressure usually remains at about pre-operative level. After perfusion the arterial pressure is measured directly from a catheter in the femoral artery; it is at this stage, until the conclusion of surgery, that the estimation of arterial pressure is most valuable.

Central venous pressure.

This is the most important single index of the body blood volume. During perfusion it is kept at pre-perfusion level by addition of blood from the machine reservoir when necessary. Immediately after perfusion the central venous pressure is taken as the principal guide to the adequacy of transfusion: if the central venous pressure is normal and the arterial pressure is not unduly low, the blood volume is regarded as satisfactory irrespective of the results of blood balance calculations. We consider this to be an important point; the precise measurement of the volumes of blood lost and replaced is open to many inaccuracies (see below), particularly when very large quantities of blood are involved, and in our experience it is much better to be guided by the venous pressure than by hasty calculations.

The electroencephalogram.

The changes occurring during deep hypothermia have been described by Benazon (1960). In our cases, return to a normal e.e.g. pattern has not always been immediate after rewarming of the patient. Sudden changes in the e.e.g. pattern are occasionally of value in diagnosing gross circulatory inadequacy, for example, as a result of kinking of the perfusion lines or great vessels but on the whole the e.e.g. gives little information that cannot be elicited by other means.

The electrocardiogram.

The action of the heart is best observed directly, but the e.c.g. is useful in the precise diagnosis of rhythm disturbances: for this purpose lead II is employed. Varying degrees of heart block may occur after suture of the ventricular septum; such damage to the conducting mechanism may cause temporary block, due to oedema, or permanent atrioventricular dissociation. Other arrhythmias are common during rewarming.

Many rhythm disturbances disappear with adequate rewarming and replacement of lost blood but the use of a pacemaker or isoprenaline may be necessary in heart block. In the post-perfusion and immediate postoperative periods, the e.c.g. is essential for the detection of rhythm changes, for the control of digitalization and for the treatment of residual heart block.

Blood chemistry.

The pH of the blood is measured before, during and after perfusion. With high perfusion rates we have found that the blood pH rarely falls below 7.3, even after more than an hour of circulatory arrest. It must be made clear, however, that these pH measurements have been made at normal body temperature: if corrected for profound hypothermia they would rise by approximately 0.2 but the significance of blood pH and other biochemical constants at low temperatures is not precisely known.

BLOOD BALANCE

Measurement of loss.

As described above, the patient is weighed before and after operation, allowance being made for the weight of dressings and the volume of urine removed if the patient is catheterized at the end of the operation. Throughout the operation, swabs are weighed: the majority of these swabs are used dry but if saline or other solutions are put out by the nursing staff the volumes of these are noted. All blood removed by suction, from the thorax and from inside the heart, is led into a graduated cylindrical flask at the anaesthetist's eye level: this flask can be drained periodic-

ally into a graduated Winchester jar (fig. 2). At the end of the operation, when a final blood balance has been made, suction is transferred to the graduated chest drainage bottle (also of cylindrical shape) with which the patient returns to the ward. In addition, blood volume estimations have been made in some cases by means of red cells tagged with radioactive chromium.

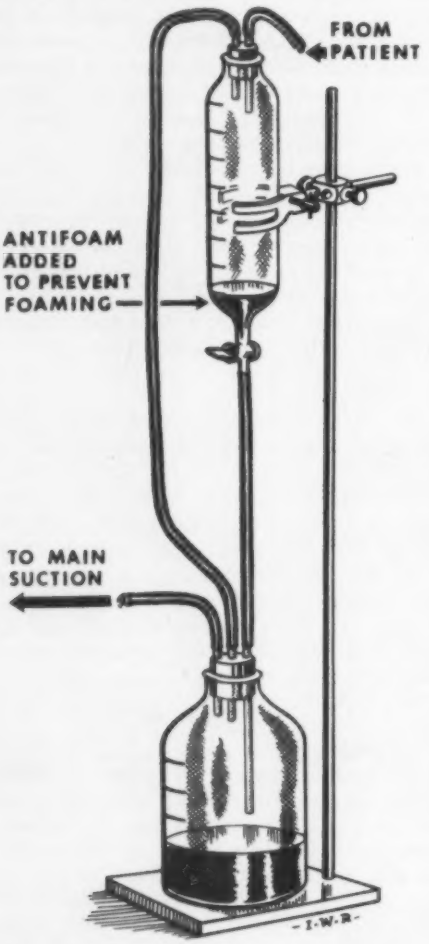

FIG. 2

Suction arrangement used during extracorporeal circulation procedures. The upper receiving cylinder is close to the anaesthetist, at eye level, and receives all blood aspirated during the operation. It is emptied at intervals into the large bottle below.

Sources of error.

Blood may be lost on to the surgeon's gown, the sterile towels and the operating theatre floor; saline and heparin-saline solutions may be lost in the same way. During connection and withdrawal of the cannulae, blood may be lost from the patient or from the pump-oxygenator. During perfusion, oedema fluid may be returned from the patient to the pump; there may be some leakage from connections, and with a large pump-oxygenator, holding several litres of blood, it is difficult to be accurate to within 100 ml in assessing the final pump blood volume.

Even if blood loss is measured fairly accurately, it does not always follow that the same quantity should be replaced. During deep hypothermia vasomotor tone is lost and the intravascular capacity of the body increases (Mustafa Oz, et al, 1960); repair of a complex intracardiac defect may bring about a sudden and radical change in haemodynamics. During rewarming, and after correction of the defect, it is sometimes apparent that although calculations suggest that blood replacement has been adequate the patient is clinically undertransfused. In these circumstances supplementary transfusions are given from the pump-oxygenator before the femoral cannula is removed until the tone of the heart, the central venous pressure and the femoral arterial pressure are satisfactory.

When the heart has resumed control of the circulation effectively after perfusion, blood loss is made good as it occurs by the intravenous route. This is a period of the operation during which constant vigilance is essential, since until cannulae are removed and the effects of heparin are fully counteracted blood loss may be very considerable and this loss may persist in the early postoperative period. For this reason postoperative weighing of the patient and return to the ward should be as expeditious as possible: reliance must not be placed on simple underwater seal drainage because unless suction is applied concealed blood loss may occur within the chest.

Varieties of blood.

The blood used for priming the pump-oxygenator is collected not more than two days before the operation, and is prevented from clotting by admixture with EDTA (ethylene-diamine-

tetra-acetic acid) which removes free calcium ions. Before use, heparin and calcium ions are added. Full blood studies are carried out pre-operatively on each patient and, if any coagulation defect is revealed, only fresh heparinized blood is used. For the replacement of blood loss after perfusion and in the early postoperative period, we use fresh blood collected anaerobically into sealed plastic bags in order to prevent loss of platelets. These bags can be used with ordinary plastic drip tubing and a Martin's pump, and the amount that has been transfused from any given bag can be measured by hooking the bag to a small spring balance which hangs from the drip stand (fig. 1). Stored citrated blood of the appropriate group is also crossmatched and made available: this blood is used, if necessary, to replace losses before perfusion begins and it also forms a useful reserve for the post-perfusion period in case blood loss is very large. Concentrated solutions of platelets and fibrinogen are available in case haematological studies at the end of perfusion indicate that they should be used.

DISCUSSION

After the induction of anaesthesia, while breathing an oxygen-rich mixture, these patients appear pink and vasodilated, with a normal or slightly reduced blood pressure. In patients with high pulmonary vascular resistance, and equally balanced left-to-right and right-to-left shunting, the institution of controlled ventilation may result in a sudden fall of arterial oxygen saturation, with bradycardia and e.c.g. changes indicative of myocardial ischaemia. The anaesthetist must be aware of this possibility.

When perfusion begins anaesthesia is very light and movements of the limbs and eyes often occur. When the perfusion flow rate has been adjusted to the maximum attainable, and particularly if trimetaphan has been given, the skin looks pink and vasodilated and the arteriocapillary refill is brisk. The clinical picture remains the same despite the fall in body temperature until the circulation is arrested. The pupils dilate widely if trimetaphan is given and remain dilated during circulatory arrest and rewarming. When perfusion is discontinued for performance of the intracardiac operation, blood gradually drains out of the dilated vessels of the face and this takes on a white-blue mottled appearance resembling post-mortem lividity. As soon as perfusion recommences the still dilated vessels fill with oxygenated blood and the face is immediately suffused with a bright pink colour which persists throughout rewarming.

After perfusion the restoration of a clinically adequate blood volume and complete re-expansion of the lungs are essential. If the surgical repair has been successful there should be no untoward events during closure of the chest. If perfusion has been adequate, if there has been no period of prolonged hypotension, and if the temperature is restored to normal, the patient should recover consciousness immediately after extubation. The incidence of respiratory complications has been no higher than after normothermic perfusion and there has been a notable absence of intrabronchial secretion at the end of the operation.

In this series patients have been subjected to periods of up to 75 minutes of circulatory arrest, at temperatures between 10°C and 13°C; there have been no apparent ill effects, and postoperative electroencephalograms have shown no change.

Other centres have reported postoperative psychoses and other cerebral complications after deep hypothermia with circulatory arrest (Björk and Hultquist, 1960). Indeed, some experienced workers now limit the period of circulatory occlusion to not more than 45 minutes. In one of our cases, a girl of 19 whose personality was somewhat unstable, an acute psychosis developed in the week following operation but this quickly recovered and appeared to be no different from the mental disturbances which are occasionally reported after other forms of surgery. With the exception of this case we have not seen cerebral complications. At the moment the causes of cerebral damage during profound hypothermia with circulatory occlusion are unknown, although the occurrence of capillary thromboses has been suggested (Björk and Hultquist, 1960). There is also some evidence that perfusion of the normothermic brain with very cold blood, or alternatively, perfusion of the cold brain with warm blood at the commencement of rewarming, may have deleterious effects (Drew, 1961). As mentioned above, we have taken care in our cases to ensure that perfusion is started with blood at body temperature and that, at the commencement of

rewarming, perfusion begins with blood at 10–12°C.

As far as we are aware, the use of trimetaphan for extracorporeal circulation cases has not been described before. In our experience it certainly appears to help in maintaining high perfusion flow rates and, if the total "circulating blood volume" (that is the volume in the pump-oxygenator, the arterial and venous lines, and the patient) is appropriately adjusted, the mean arterial pressure does not fall significantly. The chief disadvantage of trimetaphan is that the duration of its action is uncertain: we have not experienced any additional difficulty in adjusting the patient's blood volume after perfusion since using trimetaphan but the persistence of wide dilatation of the pupils in the early postoperative period is disconcerting to the uninitiated and destructive of a useful physical sign. The advantage of using halothane to ensure vasodilatation is that it can be washed out of the body through the lungs, or indeed, through the oxygenator, so that the duration of its action is more controllable; but against this must be weighed the danger of myocardial depression.

With the above technique 37 patients have now been operated on at 20°C or below; all but 3 of these cases have been subjected to periods of complete circulatory arrest, ranging from less than 45 minutes (13 cases) to over an hour (11 cases). The minimum oesophageal temperature has been below 15°C in 29 cases, and below 12°C in 12 cases.

With increasing experience of the technique we are now using these lower temperatures routinely. We have also operated on 1 case of atrial septal defect at 25°C and 1 case of pulmonary stenosis at 27°C. Fatalities have occurred but most of these have resulted from attempts to repair extremely complex congenital defects; for example, there have been 4 cases of transposition of the great vessels, all of which died. On the other hand, 4 of our 5 cases of tetralogy of Fallot and all of our 7 uncomplicated cases of ventricular septal defect have survived. There has been no mortality or morbidity attributable to the anaesthesia, or to the technique of profound hypothermia with circulatory occlusion. Full details of the series will be published by the Nuffield Department of Surgery (Gunning, in preparation).

ACKNOWLEDGMENTS

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THE FIRST EUROPEAN CONGRESS OF ANESTHESIOLOGY

will be organized by the Austrian Society of Anesthesiology in Vienna from September 3 to 7, 1962.

The former Imperial Palace will serve as the meeting place, where there will be a Scientific Congress as well as a Postgraduate Medical Training Course.

English, French and German will be the working languages. Provision will be made for simultaneous interpretation.

The main subjects of the Scientific Congress are:

(1) Watch Stations and Special Care Units.
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(3) Anaesthesia Problems in Acute Surgery (Accident Problems excluded).
(4) Free Papers (10 to 15 minutes) in limited numbers.

This programme will be supplemented by a series of Symposia on specific problems of anaesthesia and related questions. Participants who wish to organize a Symposium (about 90 to 120 minutes) should contact the Scientific Secretary—who will also furnish any other information in relation to the scientific programme—by September 30, 1961, at the very latest. These participants should indicate, at the same time, the subject of their Symposium as well as the names of the intended discussants (address: Dr. Karl Steinbereithner, Postgraduate Medical School, 4 Alserstrasse, Vienna IX).

A preliminary programme will be circulated in the autumn of 1961. It will include registration forms. For information kindly apply to the Secretary General, Dr. Rudolf Kucher, address as above.

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THREE CASES OF APPARENT RECURARIZATION

BY

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RECURARIZATION, or the re-establishment of neuromuscular block due to nondepolarizing relaxants after its apparent reversal by neostigmine, is recognized as a possible delayed complication of the use of relaxants in anaesthesia (Foldes, 1960). Although Klavis (1954) discussed the possible occurrence of recurarization, only a few cases have been reported in the literature (Speirs, 1954; Joske et al., 1954; Montgomery and Bennett-Jones, 1956; Feldman, 1959).

This paper reports three cases in whom apparent recurarization occurred. The term "apparent recurarization" is used deliberately as there is no clear proof that the clinical pictures of the cases were due entirely to the prolonged presence of gallamine triethiodide. A number of other factors may have combined to simulate the condition of curarization at some time subsequent to operation.

CASE HISTORIES

Case 1. A male, aged 71, was admitted as an emergency in January 1960, with acute appendicitis. He gave a long-standing history of angina, but had not suffered any attacks in the year prior to admission. On examination, he was of stout build, emphysematous with crepitations at the lung bases. His pulse rate was 140/min and his blood pressure was 160/100 mm Hg. There was no evidence of congestive cardiac failure. He was not clinically dehydrated. His blood urea was 38 mg per cent.

Operation was performed 2 hours after admission and a gangrenous appendix was removed.

Atropine 0.6 mg was given 1 hour prior to operation. After inhalation of 100 per cent oxygen, anaesthesia was induced by inhalation of cyclopropane with 5 per cent carbon dioxide in oxygen. When he was anaesthetized, suxamethonium 50 mg was given, the trachea sprayed with 3 ml of 4 per cent lignocaine, and intubation was carried out with a no. 10 Magill cuffed endotracheal tube.

When good respirations were re-established, intravenous gallamine triethiodide 160 mg was given and intermittent positive-negative (subatmospheric) pressure respiration (−5 cm H_2O negative phase) commenced using nitrous oxide and oxygen (6 l./min: 3 l./min) in the open circuit of the Blease Pulmoflator. One further dose of gallamine 40 mg was necessary during the operation. Atropine 0.6 mg was administered intravenously on closure of the peritoneum and residual curarization reversed with neostigmine 2.5 mg given intravenously in interrupted doses. The anaesthetic lasted 90 minutes.

His condition throughout operation had given rise to no anxiety. A considerable amount of secretion was aspirated from the trachea at extubation; at the time this secretion was thought to be due to the effect of neostigmine. He was fully conscious within 5 minutes and his respirations were judged to be normal. Lying on the trolley, the patient became a little cyanosed. Oxygen relieved this and, in the absence of further abnormal signs, he was returned to the ward with instructions for him to be propped up in bed. As his colour remained good, oxygen therapy was discontinued.

During the next three-quarters of an hour, dyspnoea became apparent. It eventually led to a diagnosis of acute pulmonary oedema. Immediate treatment with aminophylline gave no improvement, and lanoxin 0.5 mg and morphine 10 mg were administered intramuscularly. The e.c.g. tracing showed a sinus tachycardia with evidence of an old posterior infarction. His condition improved gradually and the chest signs cleared markedly.

Two and a half hours after operation, he was obviously getting drowsy, his respirations were laboured and a degree of hypotension had developed. At first, this was thought to be a morphine effect, and two doses of nalorphine 5 and 7.5 mg were given at 2 hours' interval, but there was no improvement. Gross respiratory pathology was excluded on physical examination of the chest. About 5 hours after operation, the respirations were thought to be similar to those of a partially curarized patient and this was considered seriously. Atropine 0.3 mg followed 3 minutes later by two doses of neostigmine 0.5 mg was given intravenously. The effect was almost immediate; respiration returned to a normal pattern within 5 minutes.

There was no immediate improvement in his level of consciousness or in the degree of hypotension. There was no evidence of peripheral circulatory failure; his extremities were warm and moist with venous dilatation, and the pulse volume was good. This, with the narcosis, seemed to be due to carbon dioxide build-up, consequent on an unduly prolonged period of inadequate ventilation. Over the next 2-hour period, with normal respirations, there was a gradual return of full consciousness, a noradrenaline drip was used to counteract the hypotension.

Six and a half hours after operation, he was catheterized and 30 ml of bloodstained, concentrated urine were obtained. Subsequent release of the catheter 4-hourly showed a return of satisfactory urine secretion.

Supportive therapy was continued, and there were no further "recurarizing" episodes. Postoperative electrolyte estimations were within normal limits—serum potassium concentration was 4.6 m.equiv/l. the following morning. He was discharged 17 days after admission "feeling extremely fit".

Case 2. A female, aged 49, was admitted in July 1960, giving a history of bilateral loin pain for 1 year. A left pyelolithotomy had been performed in 1955. There were no abnormal physical signs apart from bilateral loin tenderness. Blood examination showed a haemoglobin level of 73 per cent and a urea concentration of 51 mg per cent. The report on the intravenous pyelogram read: "Right kidney showed a staghorn calculus with calculi in all minor calyces. Slight contrast, outlining hydronephrotic calyces around some calculi. Left kidney showed several calculi in upper and lower calyces with fairly good contrast secretion."

Left pyelolithotomy was performed; old abscesses were found at the lower pole of the kidney.

She was given morphine 10 mg and atropine 0.6 mg 1 hour before operation. Anaesthesia was commenced by giving cyclopropane in oxygen until she was asleep. Gallamine triethiodide 120 mg was given intravenously and the trachea was intubated with a no. 7 Magill cuffed endotracheal tube. Anaesthesia was maintained using a mixture of nitrous oxide and oxygen (2 l./min:1 l./min), using carbon dioxide absorption and intermittent positive pressure respiration with the Blease Pulmoflator. Two increments of 40 mg of gallamine intravenously were necessary during the operation. Her condition throughout was satisfactory. Atropine 0.6 mg was given intravenously about 10 minutes before neostigmine 2.5 mg in interrupted doses for reversal of residual curarization. The total anaesthetic time was 95 minutes. The patient was conscious on leaving theatre and her respiratory activity was considered to be normal. Morphine 10 mg was given 3½ hours after operation because of pain.

Ten hours after operation, it was reported that the patient had been "feeling very weak" for at least 2 hours. She was seen immediately, and a generalized muscular weakness with ptosis, slight tracheal tug and depressed respirations was noted. She was fully conscious and there was no distress. A slight degree of dyspnoea had been present for 1 hour, which improved when she sat up in bed. It was not possible to obtain an immediate serum potassium estimation or an e.c.g. tracing.

A presumptive diagnosis of "recurarization" was made. Neostigmine 0.5 mg preceded by atropine 0.6 mg was given intravenously, and within 5 minutes the subjective and objective improvement was obvious. A further 0.5 mg neostigmine was given subcutaneously.

As she had not passed urine since operation, she was catheterized and 570 ml of urine obtained (S.G. 1003). The serum potassium was 4.05 m.equiv/l. the following morning, and there was no evidence of hypokalaemia in subsequent estimations. There was no further relapse, and her postoperative progress was satisfactory.

Three weeks later, right pyelolithotomy was performed under halothane anaesthesia using suxamethonium as a relaxant for intubation; it was noted that the "kidney looked unhealthy".

Case 3. A female, aged 32, was admitted as an emergency in November 1960, with intermittent heavy vaginal bleeding for over 5 weeks, and severe lower abdominal pain. There was a past history of chronic nephritis, first diagnosed in March 1960; of rheumatoid arthritis for 18 years, on cortisone therapy since March 1960; and of a uterine dilatation and curettage on two occasions for persistent menorrhagia.

On admission, she was thin and anaemic (haemoglobin 64 per cent and 53 per cent 3 days later); rheumatoid changes of the joints were present. Her pulse was regular and blood pressure was 120/70 mm Hg. Later readings showed 170/100 and 150/100 mm Hg (a persistent hypertension was noted on previous admissions in March and July 1960). There was lower abdominal tenderness and guarding, and bulky adnexae with blood in the vagina were noted. Repeated examination of the urine showed protein in large amounts, occasional hyaline casts and red blood cells; there was a small amount of reducing substance present. Four months previously, the blood urea concentration had been found to vary between 73 and 118 mg per cent. She had a preoperative transfusion of three bottles of whole blood and laparotomy was performed under cortisone cover. At operation, a left tubal pregnancy was found, and bilateral salpingo-oöphorectomy and subtotal hysterectomy were performed in view of the patient's menorrhagia and medical condition.

Morphine 10 mg and atropine 0.6 mg were given 1 hour prior to operation. Anaesthesia was induced by injecting 175 mg of 5 per cent thiopentone followed by 80 mg of gallamine triethiodide intravenously; the trachea was intubated with a no. 9 Magill cuffed endotracheal tube. Maintenance was by manual intermittent positive pressure respiration using nitrous oxide and oxygen (6 l./min:3 l./min) in a to-and-fro circuit with carbon dioxide absorption. Increments of gallamine, 20, 40 and 20 mg intravenously, to a total of 160 mg, were necessary. Pethilorfan 30 mg in divided doses was added. Her condition throughout operation gave rise to no anxiety. On closure of the peritoneum, 0.9 mg of atropine was given intravenously, followed by 2.5 mg of neostigmine at the end of the operation for reversal of residual curarization. Respirations were judged to be normal and the patient was conscious within 5 minutes. The total anaesthetic time was 75 minutes.

One dose of morphine, 10 mg, was given for sedation 4 hours after operation.

Five hours after operation (6.30 p.m.), she was seen because of tachycardia, 120/min, and sweating.

8 p.m. Pulse rate 140/min; blood-pressure 130/100 mm Hg. At this stage, she complained that she was unable to move her legs; this was ascribed to her arthritis and a "postoperative weakness".

9 p.m. Pulse rate 160/min. Internal haemorrhage was suspected, but in the absence of other physical signs it was decided to continue observation.

9.45 p.m. Pulse rate 146/min; blood pressure 130/100 mm Hg; the hands and feet were warm and moist; e.c.g. showed no abnormality; 120 ml of urine were obtained by catheter. Stridor was noted and mucus sucked out of her throat; there was an inability to cough. Ptosis was noted but was attributed to "postoperative weakness". The clinical picture at this stage was "tachycardia without hypotension or signs of peripheral failure—cause unknown".

11.30 p.m. An episode of cyanosis occurred which responded to oxygen given by B.L.B. mask. Respiratory rate was 28/min. Examination of the chest showed coarse râles in both lung fields; a portable chest X-ray demonstrated no abnormality.

Midnight. Seen by a consultant anaesthetist. "There was a weakness of general musculature and she was unable to open her eyes fully. The diagnosis of recurarization was made and intravenous atropine 0.6 mg followed by 2.5 mg of neostigmine were given. The response was dramatic. Before treatment, an attempt to record the minute volume on the Dräger volumeter was not possible as the patient would not tolerate the mask on her face, but it was recorded at 6 l./min within 10 minutes of injection. The patient volunteered that she felt better, she could keep her eyes open and there was a return of muscle power."

12.45 a.m. Atropine 0.6 mg and neostigmine 2 mg given intramuscularly.

11 a.m. (21 hours after operation). She was seen again because of ptosis, diplopia, muscle weakness, inarticulation, salivation and tracheal tug with depressed respiration. The serum potassium concentration was 5.4 m.equiv/l. Further doses of atropine and neostigmine 2 mg were given intravenously, with subjective and objective improvement. The minute volume increased from 8 to 10 l./min. The blood urea concentration at this time was 97 mg per cent.

Thirty hours after operation, one further episode of weakness, etc., occurred which again responded to the injection of atropine and neostigmine, 2 mg intravenously. Serum potassium was 5.5 m.equiv/l., with no evidence of hypokalaemia on e.c.g. Again the minute volume rose from 8 to 10 l./min.

There were no further episodes of weakness.

Summary of urine secretion (case 3)

Hours post-op.	Quantity ml	Rate ml/min	S.G.
8	120	0.25	1020
23	180	0.2	—
26½	30	0.15	1018
30	105	0.5	1010
33	60	0.3	1012
37	60	0.25	1010
41	130	0.54	1015
45	120	0.5	1010
52	180	0.43	1010

DISCUSSION

The three cases described presented varying clinical features which caused much difficulty in diagnosis. The predominating signs were increasing respiratory distress and narcosis (case 1), and gradually increasing muscular weakness (cases 2 and 3) with eventual respiratory distress (case 3).

It must be stressed that reversal of initial curarization by neostigmine was considered complete before the patients were returned to the wards. Except in case 1, there was a considerable period of apparent "normality" before abnormal physical signs developed.

Several causes for these incidents were considered before a tentative diagnosis of "recurarization" was made. The dramatic response to neostigmine confirmed the presence of some form of nondepolarizing block of the neuromuscular junction in each case. Numerous factors may have been operative in simulating or causing such a block subsequent to operation and these are discussed.

A recent valuable leading article (*Lancet*, 1961) discussing postanaesthetic respiratory insufficiency stated that "Carbon dioxide narcosis gives rise to a syndrome of respiratory insufficiency which is not readily distinguished by ordinary clinical examination from curarization. Indeed, anaesthesia and operation are associated with so many factors that tend to disturb carbon dioxide elimination, that such disturbance may be the commonest cause."

Clinical signs suggestive of carbon dioxide build-up were present in cases 1 and 3, but not in case 2. These signs were a feature of the later stages of the clinical pictures and it is suggested that they were secondary to the respiratory insufficiency induced by a redeveloping neuromuscular block, rather than that carbon dioxide build-up was the cause of this respiratory insufficiency and muscle weakness. Unfortunately, estimations of alveolar carbon dioxide and minute volume measurements were not made, but the dramatic response to neostigmine in all cases, especially that shown by the increase in minute volume in case 3, was regarded as supporting the hypothesis of recurarization rather than of carbon dioxide build-up effect.

Gray and Halton (1948) have drawn attention to the possibility of sensitivity to curare. This must be considered, together with latent myasthenia gravis. If either condition was present, the initial dose of gallamine would have had a pronounced and prolonged effect. This did not occur, and further doses of relaxant were necessary during each operation. An opportunity to test the presence of latent myasthenia was missed at the second operation in case 2, and a follow-up test in case 3 was considered unjustified.

Muscular fatigue has been observed to produce an enhancement of the effect of curare (Schmidt

and Chase, 1947). This could have been a factor in case 1—the respiratory distress of acute pulmonary oedema with its prolonged respiratory muscular overactivity may have predisposed to a reparalysis (Foldes, 1960). There was no increase of muscular activity in cases 2 and 3 prior to the onset of weakness, but in case 3, with the development of respiratory distress, muscular fatigue later may have enhanced the effects of any residual gallamine.

Hypokalaemia may produce a clinical picture of lethargy, apathy, muscular hypotonicity, anorexia and nausea, often abdominal distension and dependent oedema (Le Quesne, 1957). Foldes (1957) and Feldman (1959) suggested that hypokalaemia may result in an enhanced sensitivity of the neuromuscular junction to nondepolarizing agents during the postoperative period, which could result in a re-paralysis at a concentration of relaxant previously too low to cause obvious weakness. Pre-existing potassium deficiency is not suggested by the case histories (though it was possible as a result of both chronic nephritis and steroid therapy in case 3). Estimations were not performed pre-operatively nor at the time of the complications, but the succession of normal values subsequently obtained suggests that potassium deficiency was not a factor. In case 3, the development of hypokalaemia was excluded in the later episodes.

Marsh (1952) postulated that if there was later dehydration or electrolyte or fluid shift, sufficient relaxant might be mobilized back into the plasma from extravascular sites to bring about further paralysis. Since gallamine is distributed to these sites after administration (Kalow, 1959), this might have been a factor, but there was no evidence that postoperative dehydration or fluid shift had occurred in these cases.

Streptomycin in large doses and neomycin in normal doses have been cited as causing a nondepolarizing block of the neuromuscular junction (Foldes, 1958; Loder and Walker, 1959). An increased sensitivity to gallamine could have occurred if these drugs had been given. However, only one dose of streptomycin of 0.5 g had been administered in cases 1 and 2 and none in case 3.

Hypothermia has been quoted as a possible cause of recurarization (*Lancet*, 1961). There is experimental evidence (Bigland et al., 1958) which suggests that recurarization may occur on rewarming a hypothermic patient who has received neostigmine as an antidote to d-tubocurarine. No evidence has been given with reference to gallamine, but this cause is untenable in these cases.

The clinical picture in all three cases was not that of an exaggerated response to morphine, though it was considered in case 1.

The dose of neostigmine to reverse curarization may have been inadequate (Speirs, 1954). On a time basis, this could be considered as a factor in case 1 only. Under normal circumstances, a dose of 2.5 mg of neostigmine should have been sufficient both to reverse the action of 200 mg of gallamine at the end of an operation lasting 90 minutes, and to cover the period required for its excretion.

Foldes (1960) suggests the possibility that redistribution of anticholinesterase (neostigmine) from the motor endplate may occur before the relaxant displaced by it has been excreted or detoxified. This could occur as a result of an increased rate of "loss" of anticholinesterase with a normal rate of excretion of relaxant, or of normal redistribution of anticholinesterase with a decreased rate of excretion of relaxant. It is suggested that the latter possibility occurred in these cases. There was a normal redistribution of neostigmine (including its hydrolysis and excretion), but because of defective renal function, a sufficient concentration of gallamine remained in the circulation to re-establish a neuromuscular blockade.

Gallamine is excreted unchanged in the kidneys (Mushin, et al., 1949) and any disturbance of renal blood flow, glomerular filtration or tubular excretion will affect its rate of excretion. All three cases described had disturbances of one or more of these factors to a varying degree.

In case 1 the cardiovascular system was unhealthy, and in the absence of evidence of a fresh myocardial infarction, it is suggested that acute left ventricular failure, precipitated by the vagolytic effects of gallamine and atropine together with the surgical stress (Doughty and Wylie, 1951; Johnstone, 1955), resulted in a renal "shut-down". This view is supported by the observation that only 30 ml of urine were excreted by 6½ hours after operation—an excretion rate very much less than expected as part of the metabolic response to operation (Le Quesne,

1959). The resultant delay in the excretion of gallamine was probably the principal cause of "recurarization".

In addition, the increased activity of the respiratory muscles during the episode of acute dyspnoea may have predisposed to the redevelopment of a neuromuscular block.

It is suggested that the clinical picture of a carbon dioxide build-up was an effect of the state of recurarization.

In both cases 2 and 3 there was serious impairment of renal function as a result of chronic infection (case 2) and chronic nephritis (case 3). The ability of the kidneys to excrete drugs (i.e. those normally excreted by the kidneys) was probably greatly reduced. These cases add emphasis to the opinion of Montgomery and Bennett-Jones (1956) that "Renal failure may so delay excretion of the relaxant (gallamine triethiodide) that repeated doses of neostigmine may be required over a period of 24 hours, or possibly even longer, postoperatively", and that the use of relaxants excreted solely by the kidneys should be avoided in patients manifesting severe renal dysfunction. Renal damage due to chronic pyelonephritis is widespread from an early stage in the disease (Brod, 1956) and in case 2, the degree of renal failure was underestimated prior to operation.

SUMMARY

Three cases are described in which apparent recurarization occurred at varying times after operation, following the use of gallamine triethiodide (Flaxedil) as the relaxant.

The differential diagnosis of states simulating or causing recurarization is discussed. It is suggested that the principal cause in these cases was a delay in gallamine excretion due to temporary extrinsic renal failure (case 1) and primary renal disease (cases 2 and 3).

The occurrence of a carbon dioxide build-up was probably secondary to the development of recurarization (cases 1 and 3) and added its own effects to the clinical pictures.

These cases add emphasis to previously expressed opinions that caution is advisable in the use of large doses of gallamine in patients with evidence of myocardial disease or renal failure.

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A SIMPLE HALOTHANE VAPORIZER

Measurement of Halothane and Oxygen Mixture by means of a Cyclopropane Flowmeter

BY

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THE apparatus to be described represents an attempt to develop a simple, cheap halothane vaporizer which could be used without modification of existing anaesthetic equipment and which would allow accurate but economical use of halothane. An earlier version of this vaporizer has been described (Cole, 1959) and the present model has already been referred to (Cole, 1960). The aim of the present paper is to describe the vaporizer and to record experiences of performance after extensive use by the writer and by a number of other anaesthetists to whom vaporizers have been supplied.

The vaporizer (fig. 1) consists of a metal assembly into which is screwed a 100-ml bottle with a suitable washer intervening. The projecting side tube is the oxygen inlet. Oxygen enters here, passes through ducts drilled in the metal and then through a vertical tube 8.25 cm long to escape through a jet 1.5 mm in diameter 2 cm above the bottom of the bottle. A safety valve which is spring loaded to open at 5 lb./sq. in., is set in the metal cap and is connected with the oxygen duct so that if the pressure exceeds that figure only oxygen escapes. The oxygen and halothane mixture leaves the apparatus through a metal tube which terminates in a yoke block.

Before use the apparatus is filled with halothane to a level just below the inlet pipe (about 22 ml), screwed into the cyclopropane yoke, and connected to a supply of oxygen. It is now possible to pass a halothane and oxygen mixture through the cyclopropane flowmeter. The amounts of oxygen and halothane vapour flowing per minute for different readings of the flowmeter are shown in table I. The readings were made with the halothane maintained at a temperature of 18.3°C (65°F) as this was felt to be the most useful temperature for calibration.

In use the concentrated halothane vapour is metered by the cyclopropane flowmeter and is

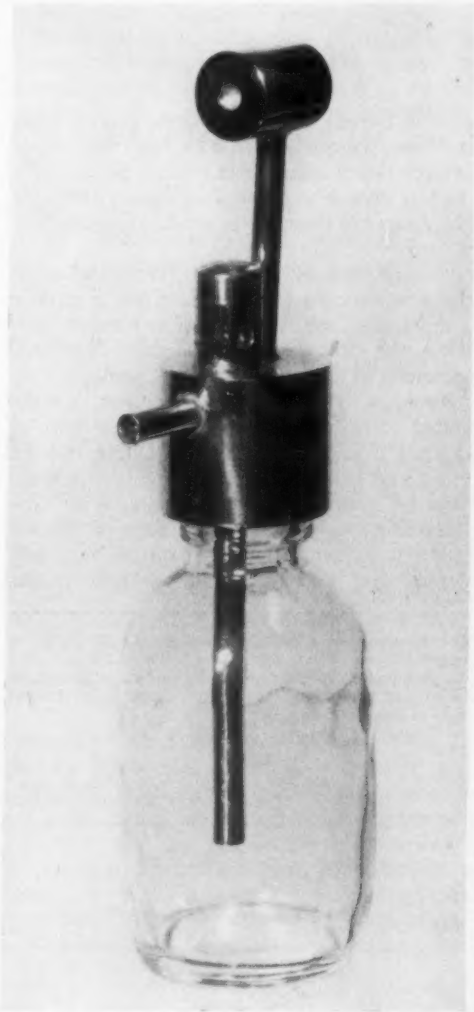

FIG. 1

TABLE I

Calibration of vaporizer at 18.3°C.

Oxygen flowrate (ml/min)	Halothane vapour (ml/min)	Cyclopropane flowmeter reading (ml/min)	Per cent concentration of vapour by volume	Liquid halothane vaporized per hour (ml)
500	158.5	800 (estimate)	24.2	42
400	113	700	22.2	30
300	90.6	500	23	24
200	50	400	20	13.2
100	25	200	20	6.6

added to oxygen and nitrous oxide passing from their own flowmeters to form an anaesthetic mixture. This is administered to the patient with a carbon dioxide absorption apparatus, except in small infants in whom non-rebreathing techniques are used.

An example might clarify the technique. Consider a robust man for an orthopaedic procedure on the lower limb. Anaesthesia is induced with thiopentone 500 mg which produces sufficient anaesthesia to allow the immediate application of a tourniquet. The inhalation anaesthetic is commenced when respiration returns, with flows of oxygen 1 l./min, nitrous oxide 2 l./min and the oxygen and halothane mixture at a cyclopropane flowmeter reading of 600 ml/min. When the rebreathing bag is half filled the rates of flow are reduced to oxygen 500 ml/min, nitrous oxide 800 ml/min* and the oxygen and halothane vapour to a reading of 500 ml/min. During the next 10 minutes the halothane mixture is gradually reduced to a flowmeter reading of 200 ml/min. When the operation has almost finished and suturing is commencing the nitrous oxide and the halothane vapour are both turned off, the oxygen is reduced to basal flow and the apparatus is wholly closed. This provides lightening anaesthesia until the completion of surgery. In making calculation it is best to think in terms of ml of pure halothane vapour flowing per minute for settings of the cyclopropane flowmeter. Changing this into percentages of the whole gas flow is then a matter of simple arithmetic.

It is, of course, possible to administer gases at different rates of flow or to close the apparatus and use only the basal rates of flow (after anaesthesia has been stabilized). The figures for maintenance of light stage 3 anaesthesia with different flows of gases are approximately as shown in table II.

It is interesting to note that, even when anaesthesia is stabilized and the system wholly closed so that no anaesthetic agent escapes, an amount

*The flow rate of nitrous oxide is measured using the carbon dioxide flowmeter. Since carbon dioxide and nitrous oxide have approximately the same molecular weight and viscosity the flowmeter reading for nitrous oxide is accepted as correct.

TABLE II

Rates of flow needed to maintain light stage 3 anaesthesia in adults.

Oxygen (ml/min)	Nitrous oxide (ml/min)	Oxygen-halothane mixture. Cyclo. flowmeter reading (ml/min)	Pure halothane vapour flowing (ml/min)	Concentration of halothane (per cent)
1,000	2,000	300	37	1.18
500	800	200	25	1.78
250	—	100–150	10–15	3–4

of 10 to 15 ml/min of pure halothane vapour must be given to maintain anaesthesia. It would appear, therefore, that halothane usage will not fall below this minimum amount which corresponds to about 4 ml of liquid halothane per hour.

DISCUSSION

Various points have been found by experience to be of importance in the operation of this vaporizer.

Difficulty has been encountered in finding a suitable washer to ensure a gastight fit between the bottle and the metal assembly. Two washers appear to be necessary; a compressible one inserted first and a tough wear-resisting washer to make contact with the bottle. The best combination so far found is a synthetic rubber washer put in first and over this a polyethylene one. If excessively rigid washers are used there is a tendency to break bottles during the screwing-in process. This tendency can be further lessened by grinding the bottle to fit the metal assembly with valve grinding compound.

It has been found that during the induction phase the greater vaporization of halothane causes the temperature of the halothane in the bottle to fall by about 5°C. During maintenance of anaesthesia the halothane regains warmth and at the end of the operation is within 2°C of room temperature. On occasions the operating room temperature has risen during the anaesthetic administration. In such cases the halothane has been warmer at the end of the operation than at the beginning. Operating theatres in Australia are usually heated in winter and cooled in summer, so that the working temperature is usually between 18.3°C and 22°C. If the apparatus were used under different temperature conditions calibration would have to be repeated for other temperatures. As a result of these temperature measurements, together with experience of the apparatus in use it is believed that with low rates of flow there is no need to make corrections for temperature variations during use.

Although the safety valve is set for 5 lb./sq.in. the apparatus is usually used with a pressure of about 2 lb./sq.in., as the tendency for leakage at the washer is less at the lower pressure. However, pressures as low as 3/4 lb./sq.in. will operate the cyclopropane flowmeter. Variations in the concentration of halothane vapour arising from alterations in pressure must occur but do not appear to be important.

The small oxygen inlet (1.5 mm) projects the oxygen as a jet on to the surface of the liquid halothane so that variations in the level of the halothane do not greatly influence the concentration of the vapour. The earlier vaporizer, which had a 5-mm inlet, gave lower vapour concentrations and showed considerable variations in concentration relative to halothane level.

Because there are no moving parts and as the specifications are easily reproducible there is no detectable variation in performance of a vaporizer at different times or between different vaporizers.

The vaporizer is easily made and probably costs less than any of the vaporizers intended specifically for halothane.

Because of the small rates of flow employed during the maintenance of anaesthesia, halothane and nitrous oxide usage are both small. The writer averages 3.75 ml of halothane per patient. There does not appear to be any damage to the apparatus from the passage through the cyclopropane flowmeter of a vapour different from the one for which it was intended.

When this vaporizer is considered in relation to the papers by Mapleson (1960), Galloon (1960), and Mushin and Galloon (1960), it will be seen that although it is designed to work with small rates of flow it is still an arrangement in which the vaporizer is outside the breathing circuit (V.O.C.) and behaves accordingly in the manner described in these papers. To some extent this vaporizer bridges the gap between the economy of the V.I.C. assembly and the controllability of the V.O.C.

SUMMARY

The conception developed by Morris (1952) of separate vaporization of liquid anaesthetics and subsequent addition of the vapour to the gaseous output of nitrous oxide and oxygen from the anaesthetic machine has been applied to halothane, using the cyclopropane flowmeter as a metering device. The apparatus is simple, cheap, and effects worthwhile economy in halothane and nitrous oxide.

ACKNOWLEDGMENTS

I wish to acknowledge the help of Imperial Chemical Industries Limited and their medical executive, Mr. Wolfe, who supplied the halothane (Fluothane) used

in the development of this apparatus, I would like to thank Professor W. W. Mushin who has kindly tested this vaporizer. The photograph was taken by Mr. Cottier, chief photographer at Victoria Eye and Ear Hospital. The vaporizers were made by Ramsden and Chaplin Limited of Melbourne (Mr. Richards, engineer).

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BOOK REVIEW

Resuscitation of the Newborn Infant. Edited by Professor Harold Abramson. Published by Henry Kimpton, London. Pp. 274; illustrated. Price 75*s.* net.

This book deals with a subject that has frequently provoked argument and discussion among paediatricians, obstetricians and anaesthetists. It suggests that of these three, the anaesthetist is "most admirably suited to lead in the development of programmes of resuscitation", a view as yet not generally accepted in this country. There is indeed very little with which the anaesthetist would disagree. The chapters on "Resuscitation procedures in the delivery room" and "drug therapy" are written with clarity and common sense. It is particularly refreshing to see some of the commonly used resuscitative procedures critically evaluated and their limitations exposed. One can agree with many of the sections, in particular those dealing with intragastric oxygen, phrenic nerve stimulation, and the principle and practice of pulmonary ventilation. If, however, the reader restricts himself to those chapters relevant to his specialty he will have grasped only a facet of this large problem.

Since twenty-four specialists have contributed to this book, the problem is viewed from many aspects. "It encompasses the investigation, early recognition, and appraisal of all influences operating before conception, during pregnancy and around the birth of the baby, and immediately after birth which may possibly contribute to perinatal distress." The dominant theme is the avoidance of foetal anoxia. The first chapters deal with the size of this problem and the underlying basic physiological and pathological causes. Maternal factors and the management of the mother during labour, including the influence of anaesthesia, are considered. Further chapters deal with resuscitation, mechanical respirators, the examination of the newborn infant, and suggestions for the layout of the recovery nursery.

The concluding chapter indicates the lines along which research and development should continue.

In a book written by so many contributors some variation in quality and style of writing must be expected, but the editor has produced a volume which is, on the whole, readable and which contains a comprehensive bibliography.

There is no doubt that if all those interested in the resuscitation of the newborn infant were to co-operate as the authors of this book have done, neonatal mortality would be reduced. This book has rendered a great service to unborn children in re-emphasizing once again the necessity for co-operation between the obstetrician, anaesthetist, paediatrician and pathologist, all of whom have vital parts to play if the infant is to survive.

Alan L. Stead

Brit. J. Anaesth. (1961), **33**, 323

DEPOSITS IN THE CYCLOPROPANE FLOWMETER

BY

F. R. RUSSELL

Hartlepools Group of Hospitals

IT is generally accepted that the control of cyclopropane on an anaesthetic machine should not depend solely on the cylinder key, as this could prove potentially dangerous if the key is turned accidentally, and indeed, accidents of this nature have been reported.

Recently, the British Oxygen Company fitted a cyclopropane fine control valve on the flowmeter block of the Boyle's machine, to eliminate this danger. However, soon after this, it was noticed that a sticky deposit was forming on the walls of the cyclopropane flowmeter tube. It was therefore necessary for the B.O.C. engineer to come at frequent intervals to clean the tube, as the bobbin would not revolve properly. Other anaesthetists had the same trouble. The B.O.C. Research Department was therefore consulted. After many experiments it was discovered that liquid cyclopropane was liable to condense in the metal connection between the cylinder and the rotameter, especially if the temperature dropped while the machine was not in use. Then, when the fine adjustment control was opened, the pressure carried this liquid cyclopropane on to the wall of the flowmeter tube. There it evaporated and left a slight deposit of grease which it had dissolved from the tubing and fittings while locked up as liquid behind the closed fine adjustment control.

The Research Department therefore suggested that the answer to the problem lay in turning off the cyclopropane at the cylinder *first* and then at the flowmeter. As an added precaution, they also recommended that at the start of a list the fine adjustment control should be opened and then closed again before turning on the cylinder valve.

OBITUARY

WILLIAM STANLEY SYKES

M.B.E., M.A.(Cantab.), M.B., B.Chir., M.R.C.S., L.R.C.P., D.P.H., D.A.

DR. W. STANLEY SYKES of Morley, Yorkshire, died suddenly on March 31. He was 67 years of age.

Stanley Sykes was born at Morley, Yorkshire, on August 5, 1894, the son of Arthur Stanley Sykes, of Morley. He was educated at Rossall and Emmanuel College, Cambridge, where he graduated M.A. He continued his medical training at St. Bartholomew's Hospital, London, qualifying M.R.C.S., L.R.C.P., in 1919, and M.B., B.Chir. in 1921. His medical studies were interrupted by the 1914–18 war. As a student he served in the Royal Navy until sent back to finish his medical course. After qualification he became House Surgeon and Extern Midwifery Assistant at St. Bartholomew's and later House Anaesthetist. Thereafter he returned to Morley where he carried on general practice. He was subsequently appointed Anaesthetist to Leeds General Infirmary, St. James's Hospital, Leeds, Leeds Dental Hospital, and Dewsbury Infirmary. He received the Diploma in Public Health in 1921, and amongst the other appointments he held were those of M.O.H., Gildersome and Drightlington Urban District Councils, District M.O., and Public Vaccinator, Morley District. In 1955 he received the Diploma in Anaesthetics of the Conjoint Examining in England Board.

In 1927 he published his first book, *A Manual of General Medical Practice*, a vade mecum for the young general practitioner; but his great love was anaesthesia. He had at this time already contributed an article on ethyl chloride to the thirteenth edition of the *Encyclopaedia Britannica*. In 1931 he published his first book on anaesthetics in the "Modern Treatment" series.

Not only was Sykes a great enthusiast and prolific writer on his own subject but his logical mind led to his writing thrillers in this period, as a relaxation. His first book, *The Mystery of the Missing Money Lender*, achieved such a popularity that it was eventually published in the Penguin series. He also wrote *The Ray of Doom*, and *The Harness of Death*.

In 1939 war again interrupted his career and he joined the 26th General Hospital R.A.M.C., as Anaesthetist in the rank of Major. Disaster overtook this unit in Greece and Sykes was a prisoner of war for the next four and a half years. He was by no means idle during this period, practising his anaesthesia under most difficult and primitive conditions, administering a hospital and inspiring his junior colleagues. He was honoured with an M.B.E. by His Majesty for his work. On his return to Leeds Sykes gave up anaesthesia completely and returned to general practice, devoting the rest of his life to the production of his chef d'oeuvre, *Essays on the First Hundred Years of Anaesthesia*, the first volume of which was published last year. The second is at the moment in the press and the remaining volumes will be published later. He retired from general practice two years ago.

Many throughout the world will regret the passing of a great friend and a brilliant colleague.

He leaves a widow and a stepdaughter.

S. G. de Clive-Lowe

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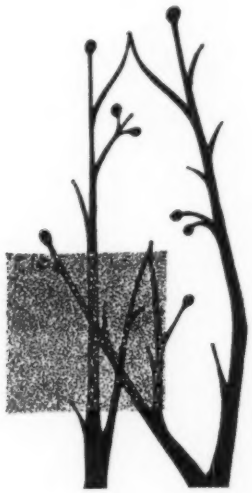

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